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(54) **Substituted trans-1,2-diaminocyclohexyl amide compounds.**

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Description

The search for strong analgesics which also possess minimal potential for dependency has been among the highest priority efforts in pharmacological research. These research efforts have, to a great extent, involved chemical modifications of the opiate structure and the discovery of chemically novel compounds which possess morphine-like activity.

The discovery of endogenous opioids has led workers in the field to consider that these peptides, possessing less rigid structures, might interact with opioid receptors other than those to which the classical rigid structure opiates, such as morphine, bind.

The concept of multiple opioid receptors has been supported by studies with nalorphine and a series of benzomorphans which display unusual pharmacological properties dissimilar from morphine, yet blocked by the selective opioid antagonists. [See, for example, W. R. Martin, et al., *J. Pharmacol. Exp. Ther.*, 197: 517—532 (1976)].

The existence of multiple types of opioid receptors is of importance because it suggests the possibility of separating the desirable analgesic and psychotherapeutic effects of a drug compound from the undesirable abuse potential or habituating effects.

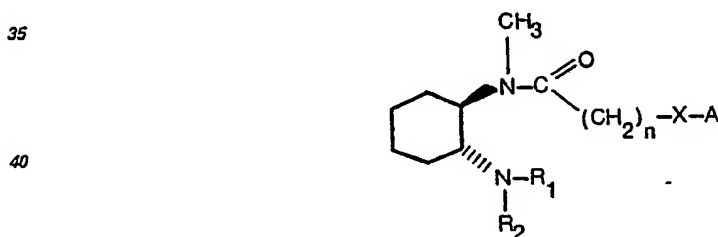
British Patent Application GB 2096607 and United States Patent 4,145,435 describe certain 2-amino-cycloaliphatic amide compounds as analgesics. In particular, *trans*-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]-benzacetamide has been reported to possess selective kappa agonist activity, and therefore to possess analgesic activity without attendant dependence liability. [See P.V. Vanvogtlander, et al., *J. Pharmacol. Exp. Ther.*, 224: 7—12 (1983)].

Recently, the diuretic effect of various opioid agonists and antagonists has been studied, and it has been shown that kappa agonists tend to increase urination, while mu agonists decreased urination. [See J. D. Leander, *J. Pharmacol. Exp. Ther.*, 227: 35—41 (1983)]. These findings suggest that selective opioid agonists and antagonists also possess potential as diuretics.

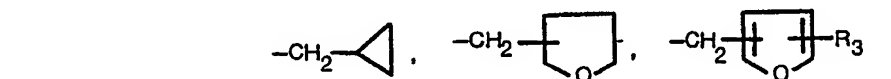
Summary of the Invention

The present invention relates to substituted *trans*-1,2-diamino-cyclohexylamide compounds useful as analgesics, diuretics, and psychotherapeutic agents. The invention is also concerned with a method of preparing such compounds, pharmaceutical compositions including such compounds, and with their use in alleviating pain in a mammal by administering an effective amount of a pharmaceutical composition in accordance with the present invention.

In its broadest aspect, the present invention encompasses compounds having structural formula I



wherein R_1 is methyl and R_2 is hydrogen, alkyl of from one to six carbon atoms



$-\text{CH}_2\text{CH}=\text{CR}_3\text{R}_4$ or $-\text{CH}_2-\text{C}\equiv\text{C}-\text{R}_4$ where R_3 and R_4 are independently hydrogen or methyl; or where R_1 and R_2 taken together with the nitrogen atom to which they are attached form a ring denoted by



where m is an integer of from three to eight; where n is an integer of from zero to six; X is oxygen, sulfur, or CHR_6 , where R_6 is hydrogen, alkyl of from one to six carbon atoms, or aryl; or X is NR_6 where R_6 is hydrogen or alkyl of from one to six carbon atoms; where A is



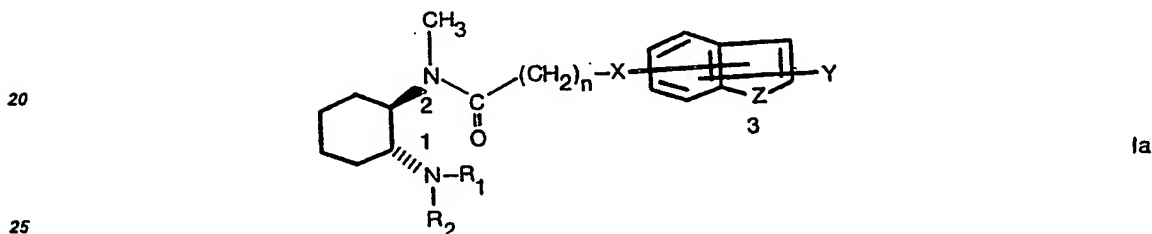
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where Y is hydrogen, fluorine, chlorine, alkyl or alkylene of from one to six carbon atoms, or aryl; and Z is oxygen, sulfur, $-\text{CH}_2-$, or NR_7 , where R_7 is hydrogen, alkyl of from one to six carbon atoms, aryl or acryl of one to six carbon atoms, or, when X is CHR_5 , R_7 is the direct bond to X; or N^1 -oxides thereof; and the pharmaceutically acceptable acid addition salts thereof.

In structural formula IIIb for subunit "A" above, the bond shown attaching the group "Y" to the fused ring system is drawn to intersect both rings of the fused ring system. This notation is meant to indicate that Y may be attached to the fused ring system at positions 2, 3, 4, 5, 6, and 7.

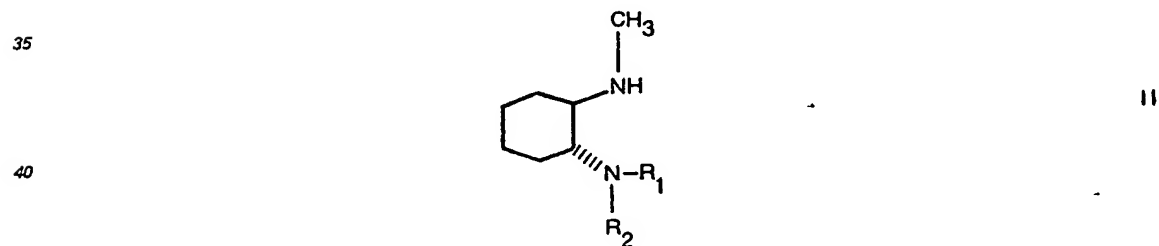
Likewise, the position of attachment of the group designated "X" to the fused ring system designated "A" may be at positions 2, 3, 4, 5, 6, or 7. Moreover, when Z is a nitrogen atom and X is CHR_5 , the nitrogen atom of the heterocyclic fused ring system may be attached by a direct bond to X.

Also contemplated as falling within this aspect of the present invention are the N^1 -oxides of compounds having structural formula I above. The meaning of the term " N^1 -oxides" is made clear by referring to structural formula Ia below in which the nitrogen atoms have been numbered. The alkyl-substituted nitrogen atom is numbered "1" and the amido-nitrogen atom is numbered "2." In these cases where Z is also nitrogen, this is numbered nitrogen atom "3."

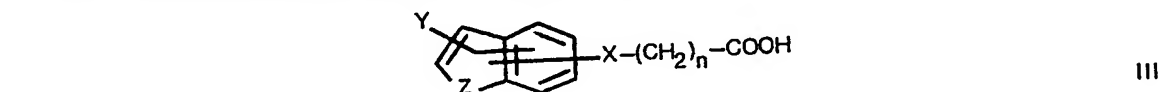


Oxidation of compounds of structural formula I above with, for example, m-chloroperbenzoic acid or other suitable oxidizing agents, readily converts the more basic alkyl-substituted nitrogen atom attached to the cyclohexane ring to its corresponding N-oxide. Throughout this specification and the appended claims, the term " N^1 -oxide" is meant to refer to these compounds.

In accordance with a second aspect of the present invention, a method of preparing compounds having structural formula I comprises reacting a substituted *trans*-cyclohexyldiamine of structure II



with a substituted carboxylic acid of structural formula III.



In accordance with another aspect of the present invention, pharmaceutical compositions useful for the alleviation of pain in a mammal comprise an effective amount of compound having structural formula I above, in combination with a pharmaceutically acceptable carrier.

In a further aspect of the present invention, we provide compounds of formula I above for use in a method of alleviating pain in a mammal which method comprises administering to a mammal suffering from pain an effective amount of a pharmaceutical composition, preferably in unit dosage form, which composition includes a compound having structural formula I, above, in combination with a pharmaceutically acceptable carrier.

Detailed Description

Compounds of the present invention comprise a class of derivatives of *trans*-1,2-diaminocyclohexane in which nitrogen is a tertiary amine nitrogen substituted with methyl and a substituent selected from the group R_2 as defined above or, preferably is a tertiary amine nitrogen attached to the cyclohexane ring and which preferably is part of a pyrrolidinyl, piperidinyl or homopiperidinyl group. The other nitrogen atom of the 1,2-diaminocyclohexane is an N-methyl amide nitrogen.

In the formula for the subunit designated "A" above, the bonds shown attaching the groups "X" and "Y" to the fused ring system are drawn to intersect both the carbocyclic and the heterocyclic rings of the fused ring system. This notation is meant to indicate that X and Y may be attached to the fused ring system at positions 2, 3, 4, 5, 6, or 7. Moreover, when Z is nitrogen, X may be attached to position 1. In those cases where Y is hydrogen, alkyl, or aryl, Y may likewise be attached to position 1 when X is attached at a position 2 through 7.

By the term "alkyl of from one to six carbon atoms" as used throughout this specification and the appended claims is meant branched or unbranched saturated hydrocarbon groupings containing one to six carbon atoms. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, n-pentyl, and the like.

By the term "aryl" is meant phenyl; phenyl substituted with fluorine, chlorine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, nitro, and trifluoromethyl; thienyl; and thienyl substituted with alkyl of from one to six carbon atoms, and alkoxy of from one to six carbon atoms.

By the term "alkoxy" is meant a branched or unbranched hydrocarbon grouping such as "alkyl" as defined above, attached to an oxygen atom.

By the term "acyl" as used herein is meant an organic radical derived from an organic acid by the removal of the hydroxy group, for example, acetyl, benzoyl, methanesulfonyl, benzenesulfonyl, p-toluenesulfonyl and the like. Thus, the term is meant to encompass alkanoyl and alkanesulfonyl where the alkyl portion is "alkyl" as defined above; aroyl and arylsulfonyl where the aromatic portion is "aryl" as defined above.

Compounds of the present invention may contain one or more asymmetric carbon atoms and thus exist as enantiomers or diastereomers. The present invention contemplates all possible optical isomeric forms of structural formula I given above. Individual enantiomeric or diastereomeric forms of the compounds of this invention may be obtained from mixtures by known methods of resolution.

In a preferred embodiment, compounds of formula I are those wherein Y is hydrogen.

In another preferred embodiment, compounds of formula I are those wherein n is zero and X is —CHR_5 , where R_5 is as defined above.

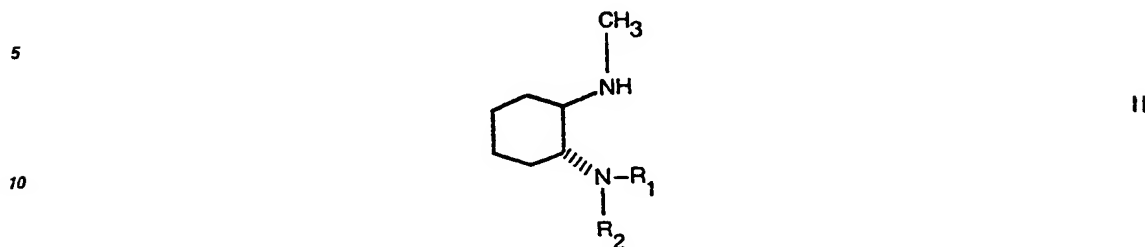
In yet another preferred embodiment, compounds of formula I are those wherein Y is sulfur or =NR_7 , where R_7 is as defined above.

Examples of compounds contemplated as falling within the scope of the present invention are the following:

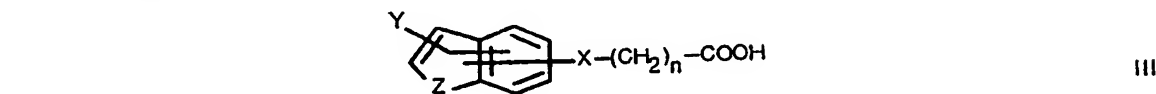
trans-N,2-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofuranacetamide;
trans-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-N-methyl-N-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(methyl(2-propenyl)amino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-N-methylbenzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(methyl(2-propynyl)amino)cyclohexyl]-benzo[b]thiophene-4-acetamide;
trans-N-methyl-7-propyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thienyl)benzo[b]thiophene-7-acetamide;
trans-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-5-acetamide;
trans-N-methyl-N-[2-(1-piperidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(methyl[(tetrahydro-2-furanyl)methyl]amino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(methyl(3-methyl-2-butenyl)amino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-[2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl]-methylbenzo[b]thiophene-4-acetamide;
trans-N,5-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-5-chloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[b]thiophene-2-propionamide;
trans-2-(benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-2-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-propanamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-butanamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-1-acetamide;
trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N,2,3-trimethyl-1*H*-indole-5-acetamide;
trans-2,3,4,9-tetrahydro-N,9-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-carbazole-6-acetamide;

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In general, compounds of the present invention are prepared by reacting the appropriate *trans*-1,2-diaminocyclohexane of the structural formula II

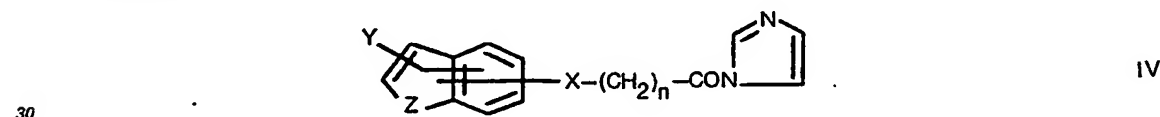


15 with a carboxylic acid of structural formula III



or a reactive derivative formed from such a carboxylic acid.

The appropriate carboxylic (III) may be reacted directly with the amine with the aid of such reagents as dicyclohexylcarbodiimide and the like. Alternatively, the carboxylic acids are first converted to a reactive derivative such as an activated ester, anhydride, acid halide such as the bromide or chloride, or acyl imidazoles of the formula IV



and the resulting carboxylic acid derivative reacted with the substituted *trans*-1,2-diaminocyclohexane (II).

For example, the reaction between the cyclic diamine (II) and the appropriate carboxylic acid (III) is carried out in the presence of the coupling reagent, dicyclohexylcarbodiimide, in a cyclic ether solvent such as tetrahydrofuran or dioxane until the desired product is formed. The reaction will generally proceed at ambient temperatures but, depending upon the reactivity of the specific materials involved, the desired reaction time, the solvent being employed, and the molar proportions of reagents, the reaction temperature may be varied between about -25°C and the reflux temperature of the solvent employed.

The reaction between the acid halide and the cyclic diamine (II) is carried out, generally at ambient temperature, in a suitable solvent in the presence of an acid acceptor such as tertiary amine or an alkali metal or alkaline earth metal carbonate or bicarbonate. The mixture of the amine and the acid halide is allowed to stand until reaction is complete.

When the reaction between the cyclic diamine (II) and the acid (III) or acid derivative has proceeded to substantial completion, the desired product is recovered from the reaction mixture by techniques well known to practitioners of the organic chemical arts.

For example, the reaction mixture can be evaporated under vacuum, if desired, to remove the solvent and other volatile components of the reaction mixture to yield the product, generally as an oil. This residual material is then taken up in a solvent such as diethyl ether, washed first with a salt solution such as sodium bicarbonate solution and then with water. Separation of the organic phase, drying over, for example anhydrous magnesium sulfate, and evaporation of the ether solvent, yields the desired product, usually as an oil or crystalline solid.

The starting *trans*-1,2-diaminocyclohexane compounds of the present invention are prepared by the method detailed in United States Patent 4,145,435. The carboxylic acids (III) are known, or if novel, are prepared by reaction sequences well known in the art. The acyl imidazole derivatives (IV) of the carboxylic acids are prepared by reacting carbonyldiimidazole with the appropriate acid.

The free base form of the compounds of this invention are readily converted, if desired, by known methods to the acid addition salts by reaction with any of a number of inorganic or organic acids including hydrochloric, hydrobromic, hydriodic, sulfuric, nitric, phosphoric, acetic, benzoic, citric, maleic tartaric, succinic, gluconic, ascorbic, sulphamic, oxalic, pamoic, methanesulfonic, benzenesulfonic, and related acids and mixtures thereof. The free base form of the compounds of the present invention and the acid addition salt may differ in certain of their physical properties, such as solubility in polar solvent, but are otherwise equivalent for the purposes of this invention.

The compounds of the present invention possess significant analgesic activity with potential for minimum dependence liability due to their selective kappa opioid receptor binding properties. In addition to analgesics, selective kappa agonists also cause opioid receptor-mediated sedation, diuresis, and

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corticosteroid elevations. Accordingly, the compounds of the present invention may also be useful diuretics and psychotherapeutic agents as well as analgesics.

Representative examples of the compounds of formula I have shown positive activity in standard laboratory analgesic tests such as writhing and hot plate with animals such as mice. For example, compounds of Examples 1 and 2 when given at 10 mg/kg s.c. (subcutaneous administration) of animal body weight, caused abolition of writhing in the acetylcholine-induced writhing test. When compared with control, mice also showed longer tolerance of heat on a hot plate at 55°C when given 10 mg/kg s.c. of the compound of Example 1.

Representative examples of the compounds of the present invention, when tested *in vitro* to determine the extent of opioid receptor binding, were found to be selectively bound to the kappa receptors with evidence of little or no binding to the mu and delta receptors. The benefits of this selective binding has already been mentioned above and is also described by M. B. Tyers, *Br. J. Pharmac.* (1980) 69:503—512.

Measurement of the kappa opioid receptor site binding activity of compounds of the present invention was made by the following method. Guinea pig brain homogenates were prepared fresh each day utilizing the method of Gillan, et al, *Br. J. Pharm.*, 70:481—490 (1980).

The binding of tritiated etorphine to brain homogenates was measured in the presence of unlabelled competitor compounds of the present invention with 200 nanomolar D-Ala-D-Leu-enkephalin (acronym DADLE) and 200 nanomolar D-Ala-MePheGly-ol-enkephalin (acronym DAGO) added to saturate the delta and mu opioid receptors, respectively. The reaction was terminated by rapid filtration and the radioactivity bound to the filters counted by liquid scintillation spectrophotometry.

Measurement of the mu and delta opioid receptor site binding activity of compounds of the present invention was made by the following method. Guinea pig homogenates were prepared fresh each day utilized the method of Gillan, et al., cited above.

Homogenates were incubated for 150 minutes at 0°C with either tritiated DAGO to measure mu receptor site binding activity, or with tritiated DADLE in the presence of a ten-fold excess of unlabelled DAGO to measure delta opioid receptor site activity. Nonspecific binding was determined in the presence of 10^{-6} M DAGO and 10^{-6} M DADLE.

Reactions were terminated by rapid filtration and the radioactivity bound to the filters counted by liquid scintillation spectrophotometry.

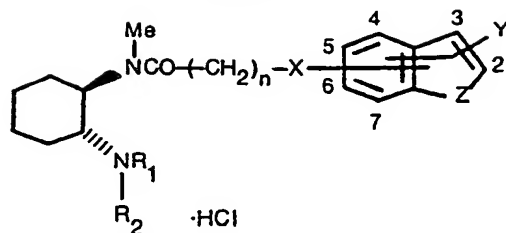
Data was analyzed by the methods of Scatchard, *Ann. N.Y. Acad. Sci.*, 51:660—672 (1949) and Hill, *J. Physiol.*, 40:IV—VIII (1910). The inhibition of binding of tritiated etorphine, DAGO and DADLE by cold ligands was determined from the regression of log percentage inhibition of specific binding or log concentration of cold ligand. The inhibition constant (K_i) was calculated from the equation:

$$K_i = \frac{IC_{50}}{1 + [L]/KD}$$

where [L] is the concentration of the labelled ligand and K_D , its equilibrium dissociation constant.

The results of these tests for several representative compounds of the present invention are presented in Table I.

TABLE 1



R1 R2	n	x	z	Y	(Ki M) Kappa	Mu
c-C ₄ H ₈	0	4-CH ₂	S	H	3.73x10 ⁻⁹	4.08x10 ⁻⁷
c-C ₄ H ₈	0	5-CH ₂	NCH ₃	2,3-c-C ₄ H ₈	3.97x10 ⁻⁶	4.67x10 ⁻⁷
c-C ₄ H ₈	0	3-CH ₂	NH	H	7.45x10 ⁻⁸	2.94x10 ⁻⁶
c-C ₄ H ₈	0	3-CH ₂	S	H	4.85x10 ⁻⁸	>10 ⁻⁶
CH ₃ , H	0	4-CH ₂	S	H	10 ⁻⁶ -10 ⁻⁷	>10 ⁻⁶
c-C ₄ H ₈	1	3-CH ₂	NH	H	>>10 ⁻⁶	>>10 ⁻⁶
CH ₃ , CH ₂ -	0	4-CH ₂	S	H	~10 ⁻⁷	10 ⁻⁶ -10 ⁻⁷
c-C ₃ H ₅						
CH ₃ , CH ₂ CH:	0	4-CH ₂	S	H	~10 ⁻⁷	2.1x10 ⁻⁷
CH ₂						
c-C ₄ H ₈	2	3-CH ₂	NH	H	>10 ⁻⁶	NT
c-C ₄ H ₈	0	3-CH ₂	O	2-CH ₃	7.89x10 ⁻⁸	~10 ⁻⁵
c-C ₄ H ₈	0	3-CH ₂	CH ₂	H	~10 ⁻⁷	~10 ⁻⁵
c-C ₄ H ₈	0	5-CH ₂	O	3-Ph	~10 ⁻⁶	~10 ⁻⁵
c-C ₄ H ₈	0	2-CH ₂	CH ₂	H	~10 ⁻⁵	~10 ⁻⁵ -10 ⁻⁶
c-C ₄ H ₈	0	7-CH ₂	S	3-(2'-	~10 ⁻⁵	NT
				thiophene)		
c-C ₄ H ₈	0	5-CH ₂	S	3-Ph	~10 ⁻⁵	NT
c-C ₄ H ₈	0	4-CH ₂	S	7-nPr	4.24x10 ⁻⁸	1.82x10 ⁻⁷
c-C ₅ H ₁₀	0	4-CH ₂	S	H	2.45x10 ⁻⁷	2.41x10 ⁻⁶
CH ₃ , 2-tetra-	0	4-CH ₂	S	H	10 ⁻⁶ -10 ⁻⁷	NT
hydrofur-						
furyl						
c-C ₄ H ₈	0	4-CHMe	S	H	>10 ⁻⁶	NT
CH ₃ , CH ₂ CH:	0	4-CH ₂	S	H	2.05x10 ⁻⁷	3.25x10 ⁻⁸
CMe ₂						

The abbreviation "c-C₄H₈" represents the divalent butylene radical. When R₁ and R₂ represent the butylene radical, then together with the nitrogen atom to which they are attached, they form a pyrrolidiny ring. The group "c-C₅H₁₀" represents the divalent pentamethylene radical. When R₁ and R₂ represent the pentamethylene radical, then together with the nitrogen atom to which they are attached, they form a piperidyl ring.

The compounds of the present invention, and/or the nontoxic, pharmaceutically acceptable salts thereof, may be administered to mammals in pharmaceutical compositions or formulations which

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comprise one or more of the compounds of this invention and/or the nontoxic, pharmaceutically acceptable, nontoxic carrier.

The compounds of this invention may be administered parenterally in combination with conventional injectable liquid carriers such as sterile pyrogen-free water, sterile peroxide-free ethyl oleate, dehydrated
5 alcohols, propylene glycol, and mixtures thereof.

Suitable pharmaceutical adjuvants for the injecting solutions include stabilizing agents, solubilizing agents, buffers, and viscosity regulators. Examples of these adjuvants include ethanol, ethylenediamine tetraacetic acid (EDTA), tartrate buffers, citrate buffers, and high molecular weight polyethylene oxide
10 viscosity regulators. These pharmaceutical formulations may be injected intramuscularly, intraperitoneally, or intravenously.

Compounds of the present invention, and/or the nontoxic, pharmaceutically acceptable salts thereof, may be administered to mammals orally in combination with conventionally compatible carriers in solid or in liquid form. These oral pharmaceutical compositions may contain conventional ingredients such as binding agents selected from the group consisting of syrups, acacia, gelatin, sorbitol, tragacanth, polyvinyl-
15 pyrrolidone, and mixtures thereof. The compositions may further include fillers such as lactose, mannitol, starch, calcium phosphate, sorbitol, methylcellulose, and mixtures thereof.

These oral compositions may also contain lubricants such as magnesium stearate, high molecular weight polymers such as polyethylene glycol, high molecular weight fatty acids such as stearic acid silica, or agents to facilitate disintegration of the solid formulation, such as starch, and wetting agents such as
20 sodium lauryl sulfate.

The oral pharmaceutical compositions may take any convenient form such as tablets, capsule, lozenges, aqueous or oily suspensions, emulsions, or even dry powders which may be reconstituted with water and/or other liquid media prior to use.

Compounds of the present invention and/or the nontoxic, pharmaceutically acceptable salts thereof
25 may be administered topically in the form of an ointment or cream containing from about 0.1% to 10% by weight of the active component in a pharmaceutical ointment or cream base.

Compounds of the present invention and/or the nontoxic, pharmaceutically acceptable salts thereof, may be administered to mammals rectally in the form of suppositories. For preparing suppositories, a low-melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active
30 ingredient is dispersed homogeneously therein by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

The solid or liquid forms may contain flavorants, sweeteners, and/or preservatives such as alkyl p-hydroxybenzoates. The liquid forms may further contain suspending agents such as sorbitol, glucose, or other sugar syrups, methyl-, hydroxymethyl-, or carboxymethylcellulose, and gelatin, emulsifying agents
35 such as lecithin or sorbitol monooleate, and conventional thickening agents. The liquid compositions may optionally be encapsulated in, for example, gelatin capsules, in an effective amount.

Preferably, the pharmaceutical compositions of this invention are in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate amounts of the active component. The unit doses form can be packaged preparation with the package containing discrete quantities of the
40 preparation. For example, the package may take the form of packeted tablets, capsules, and powders in envelopes, vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself or can be the appropriate number of any of these packaged forms.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 0.5 mg to about 350 mg according to the particular application and the potency of the active ingredient.

45 When employed systematically in therapeutic use as analgesic agents in the pharmaceutical method of this invention, the compounds are administered at doses of about 0.05 mg to 2.0 mg of active compound per kilogram of body weight of the recipient.

General synthetic methods for preparing compounds of the present invention wherein R₁ and R₂, taken together, form a pyrrolidiny ring are given below in Methods A—D. Examples 1—30 illustrate the
50 preparation of particular compounds in accordance with the present invention.

General Synthetic Methods

Preparation of amide monohydrochlorides (2 mmol scale)

Method A: *Trans-N*-methyl-2-(1-pyrrolidiny) cyclohexanamine (364 mg, 2 mmol) in methylene
55 chloride (5 ml) was added with stirring to a solution of the acid chloride [prepared by the action of thionyl chloride (5 ml) on the appropriate carboxylic acid (2 mmol)] in methylene chloride (20 ml). After stirring for ten minutes, the mixture was evaporated to small volume and diethyl ether added until no more precipitate appeared. The product was collected by filtration, washed with diethyl ether, and dried in a vacuum oven at 70°C overnight.

60 Method B: *Trans-N*-methyl-2-(1-pyrrolidiny)cyclohexanamine (364 mg, 2 mmol) in methylene chloride (5 ml) was added with stirring to a solution of the acid chloride [prepared by the action of thionyl chloride (5 ml) on the appropriate carboxylic acid (2 mmol)] in a 1:1 mixture of methylene chloride and diethyl ether (20 ml). After stirring for ten minutes, diethyl ether was added until no more precipitate appeared. The product was collected by filtration, washed with diethyl ether, and dried in a vacuum oven at 70°C
65 overnight.

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Method C: A solution of carbonyl di-imidazole (356 mg, 2.2 mmol) in dry tetrahydrofuran (10 ml) was added to a solution of the appropriate carboxylic acid (2 mmol) in tetrahydrofuran (20 ml). The mixture was stirred for 30 minutes at room temperature. *Trans-N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine (364 mg, 2 mmol) in tetrahydrofuran (10 ml) was added, the mixture heated to reflux, then stirred at room temperature for 16 hours. The reaction was evaporated to small volume, and the residue dissolved in ethyl acetate (100 ml). The extract was washed with saturated sodium bicarbonate (3 × 50 ml), then water (50 ml), dried (MgSO₄), and evaporated under reduced pressure.

Method D: Substantially as described in Method C with the exception that the mixture of reactants was stirred at ambient temperature for 16 hours rather than being heated under reflux.

The following examples are provided to enable one skilled in the art to practice the present invention. The examples are not to be read as limiting the scope of the invention as defined by the appended claims, but as merely illustrative thereof.

Example 1

Preparation of *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide

A. Preparation of 7-methyl-7-azabicyclo[4.1.0]heptane [Modification of method of T. Taguchi and M. Eto., *J. Amer. Chem. Soc.* 80, 4076 (1958)].

i. Cyclohexene oxide (Aldrich, 196.3 g 2M) was added to a 25/30% solution of aqueous methylamine (745 ml, 6M) (25% solution) dropwise with stirring and cooling in an icebath over one hour, during which time the temperature reached 46°C. The solution was stirred at room temperature overnight, and then refluxed for three hours in fume hood. The solution was cooled in an icebath and saturated with solid NaOH, extracted with 4 × 200 ml ether, dried (MgSO₄) and evaporated to dryness on rotary evaporator.

The crude product, *trans*-2-(methylamino)cyclohexanol, was distilled under water vacuum pressure, the first small sample of cyclohexene epoxide discarded. The bulk was distilled from a 1-liter flask with a 60W isomantle and a short Leibig condenser over a two hour period to yield the product.

bp 118°C (water vacuum)
yield: 208 g (81%)

ii. *Trans*-2-(methylamino)cyclohexanol (208 g 1.61 M) was placed in a three liter beaker and dissolved in ether (400 ml). Chlorosulphonic acid (1.89 g, 1.62 M) was added dropwise to the ice-salt cooled solution. Added a further 200 ml of ether. The solution was hand stirred. Addition took one hour. The solution/solid was allowed to warm to room temperature and stand for three hours. The ether was decanted and the white salt washed with 300 ml ether which was also decanted.

The solid was cooled in ice-salt bath and NaOH (218 g in one liter water) added slowly. The thick white solid was left at room temperature overnight.

The crude product, 7-methyl-7-azabicyclo [4.1.0] heptane, was distilled in isomantle with continuous addition of water from separating funnel to retain approximately original volume. After 600 ml of liquid had been collected, the total distillate was saturated with solid NaOH, extracted with 5 × 200 ml ether, dried (MgSO₄) and evaporated on rotary evaporator.

The product was distilled using a water vacuum and air bleed, the collection vessel being cooled in an ice bath.

Yield: 67 g (37%), b.p. 38°C (water vacuum and bleed)

iii. Preparation of *trans-N*-Methyl-2-(1-pyrrolidinyl)cyclohexanamine

A mixture of 7-Methyl-7-azabicyclo[4.1.0]heptane (7.0 g, 0.063 M), pyrrolidine (17.92 g, 0.25 M), water (10 ml) and ammonium chloride (0.16 g) was stirred and refluxed for 21 hours. The solution was cooled and solid sodium hydroxide added and extracted with ether (3 × 50 ml). The extracts were dried over magnesium sulphate and evaporated under reduced pressure to a brown oil. This was distilled under high vacuum to yield a colorless oil.

bp: 95°C (6.0 g)

B. Preparation of *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

By Method B, benzo[b]thiophene-4-acetic acid (192 mg, 1 mmol) was converted to the *amide monohydrochloride* (376 mg, 96%); V_{max}C = 1640 cm⁻¹.

Example 2

Preparation of *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)-*p*-cyclohexyl]-1H-indole-3-acetamide monohydrochloride

A). *Trans-N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine was prepared as described in example 1 above.

B. Preparation of *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indol-3-acetamide monohydrochloride.

Trans-N-methyl-2-(1-pyrrolidinyl)cyclohexanamine (0.368 g) was dissolved in methylene chloride (10 ml) and stirred at room temperature. The acid chloride of 3-indole acetic acid (prepared by the action of thionyl chloride on 3-indole acetic acid, 0.35 g) dissolved in methylene chloride (10 ml) was added and let stand for five hours. Ether was added to rapidly stirred solution until no more precipitate appeared. After

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further rapid stirring for one hour, the precipitate was filtered and dried in a vacuum oven at 90°C for one hour and stored in a predried bottle. The product was in the form of a black glassy solid (300 mg).

Example 3

- 5 Preparation of *trans*-*N*-methyl-*N*-(1-pyrrolidinyl)cyclohexyl)-1*H*-indole-3-acetamide free base
1*H*-Indole 3-acetic acid (1.05 g, Aldrich) and *trans*-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine were dissolved in tetrahydrofuran (30 ml) and cyclohexyl carbodiimide (1.24 g) added. The resultant solution was stirred at room temperature overnight, during which time a white precipitate appeared.

The solution was filtered and evaporated to an oil, which was chromatographed on silica. Elution with ether gave the product as a white solid (1.3 g), mp 175—178°C.

Example 4

Trans-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-propanamide monohydrochloride

- By Method C, indole-3-propanoic acid (0.752 g, 4 mmol) was converted to the *amide*
15 *monohydrochloride* (0.65 g, 42%) isolated as white crystals, mp 143.5—145°C.

Example 5

Trans-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-butanamide dihydrogen sulphate

- By Method D, indole-3-butyric acid (406 mg, 2 mmol) was treated with carbonyl diimidazole (356 mg, 2 mmol) and the diamine (364 mg, 2 mmol). After standing for 16 hours at room temperature the mixture was refluxed for a further 20 hours. The crude product was purified by column chromatography [silica gel eluted with CH₂Cl₂:EtOH:0.880 NH₃, 18:2:1, lower layer] to give the pure free base. The dihydrogen sulphate salt was then prepared by the addition of an ethereal solution of the amine, giving the product as a very hygroscopic solid (190 mg, 20%); V_{max} 1635 cm⁻¹.

Example 6

Trans-(+)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-1-acetamide

- Triethylamine (139 µl, 1 mmol) was added to a solution of 1*H*-indole-1-acetic acid (175mg, 1 mmol) in tetrahydrofuran (10 ml) at -15°C with vigorous stirring. Ethyl chloroformate (96 µl, 1 mmol) was added, and the mixture stirred for five minutes. A solution of *trans*-(±)-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine (182 mg, 1 mmol) in tetrahydrofuran (2 ml) was added, and stirring continued for 30 minutes at -15°C, then 30 minutes at room temperature. The reaction was evaporated to small volume, the residue dissolved in ethyl acetate (50 ml), and washed with saturated sodium bicarbonate solution (3 × 50 ml). The organic extract was dried (MgSO₄), evaporated under reduced pressure, and recrystallized from diethyl ether/methylene chloride to yield the *amide* (100 mg, 32%); V_{max} C = 0 1635 cm⁻¹.

Example 7

Trans-(±)-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-*N*,2,3-trimethyl-1*H*-indole-5-acetamide

- Triethylamine (139 µl, 1 mmol) was added to a solution of 2,3-dimethyl-1*H*-indole-5-acetic acid (203 mg, 1 mmol) in tetrahydrofuran (10 ml) at -15°C, with vigorous stirring. Ethyl chloroformate (96 µl, 1 mmol) was added, and the mixture stirred for five minutes. A solution of *trans*-(±)-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine (182 mg, 1 mmol) in tetrahydrofuran (2 ml) was added, and stirring continued for 30 minutes at -15°C, then 30 minutes at room temperature. The reaction was evaporated to small volume, the residue taken into ethyl acetate (50 ml), and washed with saturated sodium bicarbonate solution (3 × 50 ml). The organic extract was dried (MgSO₄), evaporated under reduced pressure and recrystallized from ethyl acetate to yield the *amide* (204 mg, 56%); V_{max}C = 0 1615 cm⁻¹.

Example 8

Trans-(±)-*N,N'*-dimethylcyclohexane-1,2-diamine

- A vigorously stirred mixture of *N*-methylazabicyclo-[4.1.0]-heptane (36.1 g), monomethylamine (162 ml of a 23—30% aqueous solution) and ammonium chloride (0.50 g) was heated in an oil bath at 94—99°C for 21.5 hours. After cooling to 0°C the mixture was treated with sodium hydroxide (10 g) and extracted with diethylether (4 × 100 ml). The combined ethereal fractions furnished a residue which was distilled to give pure *trans*-(±)-*N,N'*-dimethyl-cyclohexane-1,2-diamine (18 g, 39%); b.p. 78°C (14 mm) which solidified after standing at 17°C; found: C, 67.5; H, 13.1; N, 19.65. Calc. for C₈H₁₈N₂; C, 67.55, H, 12.75; N, 19.7.

Example 9

Trans-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

- A solution of benzo[b]thiophene-4-acetic acid (4.65 g, 24 mmol) and carbonyldiimidazole (3.95 g, 24 mmol) in tetrahydrofuran (20 ml) was heated to reflux for 0.5 hours, then cooled to 0°C and added dropwise over 25 minutes to a stirred solution of *trans*-(±)-*N,N'*-dimethylcyclohexane-1,2-diamine (3.0 g, 21 mmol) in tetrahydrofuran (10 ml) at -13°C. The mixture was stirred for a further two hours and allowed to warm to room temperature. The solvent was removed in vacuo to give residue which was dissolved in dichloromethane (100 ml) and washed with aqueous potassium carbonate (100 ml) then water (100 ml). The organic fraction furnished an oily residue which after high pressure liquid chromatography (Waters 500 Prep HPLC silica gel, 80:20:1 ethyl acetate-methanol-triethylamine) gave a light yellow oil (3.3 g); V_{max} (liquid file) 3320, 1635 cm⁻¹.

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Formation of hydrochloride salt: *Method L*: The oil (3.3 g) was dissolved in diethyl ether (100 ml), filtered through a plug of cotton wool and treated with a solution of hydrogen chloride in diethyl ether until the solution became acidic. The resulting white precipitate was isolated by filtration and washed with diethyl ether. This procedure furnished *trans*-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride (3.0 g, 40%).

Example 10

Trans-(±)-*N*-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-*N*-methylbenzo[b]thiophene-4-acetamide monohydrochloride

A solution of *trans*-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride (200 mg, 0.57 mmol) in dichloromethane (10 ml) was treated with 10% aqueous potassium carbonate to liberate the parent amine. This oil was dissolved in dichloromethane (1 ml) and triethylamine (0.15 ml, 1.1 mmol) treated with bromomethylcyclopropane (220 mg, 1.6 mmol) and heated to reflux for 26 hours. After standing at room temperature for 70 hours the mixture was poured into 10% aqueous potassium carbonate (10 ml) and extracted with dichloromethane (3 × 15 ml) to give an oil which after silica gel chromatography (100:1 ethyl acetate:triethylamine) furnished *trans*-(±)-*N*-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-*N*-methylbenzo[b]thiophene-4-acetamide (200 mg, 95%) δ_H (CDCl₃) 0.7—0.0 (5H, m); V_{max} (liquid film) 3080, 1635 cm⁻¹.

The hydrochloride salt of this oil (250 mg) was prepared as described in Method L and recrystallized (dichloromethane-diethyl ether) to give a white solid (200 mg, 73%); m.p. 229—234°C.

Example 11

Trans-(±)-*N*-methyl-*N*-[2-[methyl(2-propenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

A solution of *trans*-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride (400 mg, 1.13 mmol) in dichloromethane (10 ml) was treated with aqueous potassium carbonate (30 ml) to liberate the parent amine. This oil was dissolved in ethanol (10 ml), dichloromethane (1 ml) and triethylamine (0.3 ml, 2.2 mmol) and treated with allyl bromide (257 mg, 2.1 mmol). This mixture was stirred in an oil bath at 50—60°C for six hours, concentrated in vacuo and partitioned between 10% aqueous potassium carbonate and dichloromethane. The organic fractions furnished an oil which after silica gel chromatography (100:1 ethyl acetate:triethylamine) gave *trans*-(±)-*N*-methyl-*N*-[2-[methyl(2-propenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide (270 mg, 67%); δ_H (CDCl₃) 6.0—4.3 (3H, m); V_{max} (liquid film) 1637 cm⁻¹.

The hydrochloride salt was prepared as described in Method L and recrystallized (dichloromethane-diethyl ether) to give a white solid (170 mg; 57%); m.p. 209—211.5°C.

Example 12

Trans-(±)-*N*-methyl-2-(1-piperidinyl)cyclohexanamine

A stirred mixture of *N*-methylazabicyclo[4.1.0]heptane (5.0 ml, 39 mmol), piperidine (3.9 ml, 39 mmol) and ammonium chloride (0.2 g dissolved in 0.4 ml water) was heated to reflux for 5.5 h. Bulb to bulb distillation yielded *trans*-(±)-*N*-methyl-2-(1-piperidinyl)cyclohexanamine as a colourless liquid (oven temperature 210°/20 mm) (3.2 g, 42%); δ_H (CDCl₃) 2.34 (3H, s).

Example 13

Trans-(±)-*N*-methyl-*N*-[2-(1-piperidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

A stirred solution of benzo[b]thiophene-4-acetic acid (0.50 g, 2.6 mmol) and carbonyl di-imidazole (0.46 g, 2.8 mmol) in tetrahydrofuran (5 ml) was heated with a solution of *trans*-(±)-*N*-methyl-2-(1-piperidinyl)cyclohexanamine (0.46 g, 2.3 mmol) in tetrahydrofuran (2 ml). This mixture was heated to reflux for five minutes, concentrated in vacuo, poured into saturated aqueous sodium bicarbonate (30 ml) and extracted with dichloromethane (2 × 20 ml) to give an oil which on trituration with diethyl ether gave *trans*-(±)-*N*-methyl-*N*-[2-(1-piperidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide as a crystalline solid (610 mg, 72%); V_{max} = 0 (liquid film) 1635 cm⁻¹.

The hydrochloride salt of this amine (370 mg, 1.0 mmol) was prepared as described in Method L and recrystallized (dichloromethane-diethyl ether) to give a white solid (0.40 g, 98%).

Example 14

Trans-(±)-*N*-methyl-*N*-[2-[methyl[(tetrahydro-2-furanyl)methyl]amino]cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

A solution of *trans*-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride (120 mg, 0.34 mmol) in dichloromethane (10 ml) was treated with saturated aqueous sodium bicarbonate to liberate the parent amine. The oil was dissolved in dimethyl formamide and treated with tetrahydrofurfuryl bromide (68 mg, 0.41 mmol) and sodium bicarbonate (43 mg, 0.5 mmol). The resulting mixture was stirred in an oil bath at 95—110°C for 20 hours then concentrated in vacuo, poured into saturated aqueous sodium bicarbonate (15 ml) and extracted with dichloromethane (2 × 15 ml). Silica gel chromatography (70:30:1 ethyl acetate:hexane:triethylamine) furnished *trans*-(±)-

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N - methyl - *N* - (2 - (methyl((tetrahydro - 2 - furanyl)methyl)amino)cyclohexyl)benzo[b]thiophene - 4 - acetamide as a colourless oil (43 mg, 32%); *m/e*: 400 (M+), 329, 286, 195, 147; t.l.c. analysis of this product (50:50:1 ethyl acetate-hexane-triethylamine, multiple development) indicated that it consisted of two components.

- 5 The hydrochloride salt of this amine (42 mg, 0.10 mmol) was prepared as described in Method L to give a white solid (13 mg, 28%).

Example 15

2-(4-benzo[b]thiophene)propionic acid

- n*-Butyl lithium (4.0 ml of a 1.6 *M* solution in hexane, 6.4 mmol) was added to a stirred solution of benzo[b]thiophene-4-acetic acid (0.60 g, 3.1 mmol) in tetrahydrofuran (10 ml) and dimethyl sulphoxide (4 ml) with cooling in ice water. After 40 minutes at 0°C the resulting solution was treated with methyl iodide (190 µl, 3.1 mmol) and stirred at room temperature for 3.3 hours. Concentration in vacuo furnished a red oil which was poured into 5% aqueous sodium hydroxide (50 ml) and washed with diethyl ether (3 × 30 ml). The aqueous fraction was acidified with concentrated nitric acid and extracted with dichloromethane (3 × 50 ml) to give a red oil (0.65 g) which after silica gel chromatography (70:30 ethyl acetate-hexane + 0.5% acetic acid) gave 2-(4-benzo[b]thiophene)propionic acid as an off-white solid (0.26 g, 38%); δ_H (CDCl₃) 11.4 (1H, s); 8.0—7.0 (5H, m); 4.28 (1H, q, *J* 7 Hz); 1.62 (3H, d, *J* 7 Hz).

Example 16

- 20 *Trans*-(±)-*N*-methyl-*N*-(2-pyrrolidinylcyclohexyl)-4-benzo[b]thiophene-2-propionamide

- A stirred solution of 2-(4-benzo[b]thiophene)propionic acid (98 mg, 0.47 mmol) and carbonyl diimidazole (78 g, 0.48 mmol) in tetrahydrofuran (0.5 ml) was heated to reflux 0.5 hours then cooled to room temperature and treated with a solution of *trans*-(±)-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine (76 mg, 0.42 mol) in tetrahydrofuran (0.5 ml). This mixture was heated to reflux for 5.5 hour, poured into saturated aqueous sodium bicarbonate (30 ml) and extracted with dichloromethane (2 × 20 ml) to give an oil which after silica gel chromatography (50:50:1 ethyl acetate-hexane-triethylamine) furnished *trans* - (±) - *N* - methyl - *N*-(2 - pyrrolidinyl - cyclohexyl) - 4 - benzo[b]thiophene - 2 - propionamide (100 mg, 64%); $V_{max}C = 0$ (liquid film) 1638 cm⁻¹; t.l.c. analysis of this produce (50:50:1 ethyl acetate-hexane-triethylamine) indicated that it consisted of two components. The hydrochloride salt of this diastereoisomeric mixture of amines (80 mg, 0.22 mmol) was prepared as described in Method L to give a white solid (70 mg, 78%).

Example 17

Trans-(±)-*N*-(2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl)-*N*-methyl-benzo[b]-thiophene-4-acetamide monohydrochloride and *trans*-(±)-*N*-(2-methyl(3-methyl-2-butenyl)amino)cyclohexyl)benzo[b]thiophene-4-acetamide monohydrochloride

- A stirred solution of *trans* (±) - *N* - methyl - *N* - [2 - (methylamino)cyclohexyl]benzo[b]thiophene - 4 - acetamide (330 mg, 1.04 mmol) in dichloromethane (2 ml) was treated with 1-bromo-3-methyl-but-2-ene (140 µl) and sodium bicarbonate (160 mg, 1.9mmol) and heated to reflux for 1.5 hours. The mixture was poured into saturated aqueous sodium bicarbonate (10 ml) and extracted with dichloromethane (2 × 10 ml). Silica gel chromatography (70:30:1 ethyl acetate-hexane-triethylamine) furnished an oil (260 mg, 65%); $V_{max}C = 0$ (liquid film) 1640 cm⁻¹, which was homogeneous by t.l.c. analysis (70:30:1 ethyl acetate-hexane triethylamine) but analysis by ¹H n.m.r. indicated the presence of the parent amines of the above two compounds.

- The hydrochloride salts were formed as described in Method L and recrystallized (dichloromethane-diethyl ether) to give a white solid (0.27 g, 94%); ¹H-n.m.r. (CDCl₃) integration indicates the presence of *trans* - (±) - *N* - (2 - [(1,1 - dimethyl - 2 - propenyl)methylamino] - cyclohexyl - *N* - methyl - benzo[b]thiophene - 4 - acetamide monohydrochloride and *trans* - (±) - *N* - methyl - *N* - (2 - [methyl(3 - methyl - 2 - butenyl)amino]cyclohexyl)benzo[b]thiophene - 4 - acetamide monohydrochloride in a 5:2 ratio respectively.

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Example 18

Trans-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide monohydrochloride

- By Method A, benzo[b]thiophene-3-acetic acid (384 mg, 2 mmol) was converted to the amide monohydrochloride (716 mg, 91%); $V_{max}C = 0$ 1645 cm⁻¹.

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Example 19

Trans-(±)-*N*,2-dimethyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofurancetamide monohydrochloride

- By Method A, 2-methyl-3-benzofuranacetic acid (380 mg, 2 mmol) was converted to the amide monohydrochloride (606 mg, 78%); $V_{max}C = 0$ 1645 cm⁻¹.

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Example 20

Trans-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-3-acetamide monohydrochloride

- By Method C, 1*H*-indene-3-acetic acid (174 mg, 1 mmol) was converted to the amide. The crude product was dissolved in methylene chloride (5 ml) and treated with a solution of hydrogen chloride in diethyl ether until the solution became acidic. Diethyl ether was then added until no more precipitate appeared. The

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product was collected by filtration, washed with diethyl ether and dried in a vacuum at 70°C overnight, to yield the amide monohydrochloride (80 mg, 21%); $V_{\max}C = 0\ 1640\ \text{cm}^{-1}$.

Example 21

Trans-(±)-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofurancetamide monohydrochloride

By Method B, 3-phenyl-5-benzofuranacetic acid (252 mg, 1 mmol) was converted to the amide monohydrochloride (363 mg, 80%); $V_{\max}C = 0\ 1640\ \text{cm}^{-1}$.

Example 22

Trans-(±)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indene-2-acetamide monohydrochloride

By Method C, 1H-indene-2-acetic acid (174 mg, 1 mmol) was converted to the amide. The crude product was dissolved in methylene chloride (3 ml) and treated with a solution of hydrogen chloride in diethyl ether until the solution became acidic. Diethyl ether was then added until no more precipitate appeared. The product was collected by filtration, washed with diethyl ether and dried in a vacuum oven at 70°C overnight, to yield the amide monohydrochloride (110 mg, 29%); $V_{\max}C = 0\ 1645\ \text{cm}^{-1}$.

Example 23

Trans-(±)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thienyl)benzo[b]thiophene-7-acetamide monohydrochloride

By Method C, 3-(2-thienyl)benzo[b]thiophene-7-acetic acid (215 mg, 0.78 mmol) was converted to the amide. The crude product was dissolved in methylene chloride (3 ml) and treated with a solution of hydrogen chloride in diethyl ether until the solution became acidic. Diethyl ether was then added until no further precipitate appeared. The product was collected by filtration, washed with diethyl ether, and dried in a vacuum oven at 80°C overnight, to yield the amide monohydrochloride (200 mg, 54%); $V_{\max}C = 0\ 1635\ \text{cm}^{-1}$.

Example 24

Trans-(±)-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-5-acetamide monohydrochloride

By Method B, 3-phenylbenzo[b]thiophene-5-acetic acid (268 mg, 1 mol) was converted to the amide monohydrochloride (329 mg, 70%); $V_{\max}C = 0\ 1645\ \text{cm}^{-1}$.

Example 25

Trans-(±)-N-methyl-7-propyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

By Method B, 7-propylbenzo[b]thiophene-4-acetic acid (234 mg, 1 mmol) was converted to the amide monohydrochloride (423 mg, 97%); $V_{\max}C = 0\ 1635\ \text{cm}^{-1}$.

Example 26

Trans-(±)-2-(benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide monohydrochloride

By Method D, (benzo[b]thien-3-yloxy)acetic acid (104 mg, 0.5 mmol) was converted to the amide. The crude product was purified by column chromatography on silica, using 1% triethylamine in 1:1 hexane/ethyl acetate as elutant. The resulting solution was evaporated and the residue dissolved in dichloromethane (3 ml). A solution of hydrogen chloride in diethyl ether was added until the solution became acidic, then diethyl ether added until precipitation was complete. The product was collected by filtration, washed with diethyl ether and dried in a vacuum oven at 70°C overnight to yield the amide monohydrochloride (49 mg, 24%); $V_{\max}C = 0\ 1660\ \text{cm}^{-1}$.

Example 27

Trans-(±)-N,5-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide monohydrochloride

By Method B 5-methylbenzo[b]thiophene-3-acetic acid (206 mg, 1 mmol) was converted to the amide monohydrochloride (349 mg, 86%); $V_{\max}C = 0\ 1640\ \text{cm}^{-1}$.

Example 28

Trans-(±)-5-chloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide monohydrochloride

By Method B, 5-chlorobenzo[b]thiophene-3-acetic acid (226.5 mg, 1 mmol) was converted to the amide monohydrochloride (374 mg, 87%); $V_{\max}C = 0\ 1635\ \text{cm}^{-1}$.

Trans-(±)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-acetamide

Indole-3-acetic acid (0.7 g, 4 mmol) was dissolved in tetrahydrofuran and carbonyl di-imidazole (0.7 g) added. The solution was boiled and allowed to stand for five minutes. *Trans-(±)-N-methyl-2-(1-pyrrolidinyl)cyclohexanamine* (0.73 g, 4 mmol) was added.

The solution was refluxed for five minutes, evaporated, and washed with excess saturated sodium bicarbonate solution. The solution was extracted three times with an ether/ethylacetate mixture, the

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combined extracts with water, dried (MgSO_4), and evaporated to give the *amide* as white plates (0.76 g, 56%) mp 189—190.5°C; $\text{VmaxC} = 0\ 1605\ \text{cm}^{-1}$.

Example 29

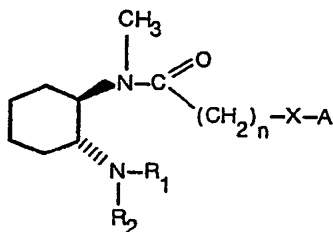
- 5 *Trans*-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-*N*-oxide-benzo[b]thiophene-4-acetamide
A solution of *trans* - (±) - *N* - methyl - *N* - [2 - (1 - pyrrolidinyl) - cyclohexyl]benzo[b]thiophene - 4 - acetamide (0.41 g) in dichloromethane (10 ml) was treated with *m*-chloroperoxybenzoic acid (100 mg) and stirred at 0°C. After 50 minutes more *m*-chloroperoxybenzoic acid (153 mg) was added and after a total of 110 minutes the mixture was poured into saturated aqueous sodium bicarbonate (20 ml) and extracted
10 dichloromethane ($2 \times 10\ \text{ml}$) to give a white solid. Recrystallization (dichloromethane — diethyl ether) furnished pure *trans*(>) - *N* - methyl - *N* - [2 - (1 - pyrrolidinyl)cyclohexyl] - *N*l - oxide - benzo[b]thiophene - 4 - acetamide (0.31 g, 72%), mp 149—151.5°C.

Example 30

- 15 *Trans*-(±)-*N*-methyl-*N*-(2-propynyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride
A solution of *trans* - (±) - *N* - methyl - *N* - (methylamino)cyclohexyl]benzo[b]thiophene - 4 - acetamide monohydrochloride (450 mg) in dichloromethane (20 ml) was treated with saturated aqueous sodium bicarbonate to liberate the parent amine. This oil was dissolved in dichloromethane (2.5 ml) and treated with propargyl bromide (250 μl of an 80% solution in toluene) and triethylamine (0.20 ml). After 17
20 hours at room temperature, potassium carbonate (200 mg) and more dichloromethane (18 ml) were added. After 1.5 days the mixture was decanted and the supernatant was treated with propargyl bromide (150 μl of an 80% solution in toluene) at room temperature. After a further 12 hours this solution was poured into saturated aqueous sodium bicarbonate (20 ml) and extracted with dichloromethane ($2 \times 20\ \text{ml}$). Silica gel chromatography (4:1 ethyl acetate — methanol containing 1% triethylamine) furnished *trans* - (±) - *N* - methyl - *N* - [2 - (methyl(2 - propynyl)amino)cyclohexyl]benzo[b]thiophene - 4 - acetamide (220 mg, 49%). Vmax liquid file 3300, 3225, 2110, 1630 cm^{-1} . The hydrochloride salt of this compound (220 mg) was prepared as described in Method I. to give a white solid (230 mg, 93%).

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

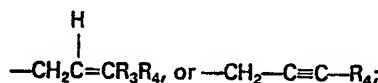
- 30 1. A compound having the structural formula



wherein:

R_1 is methyl;

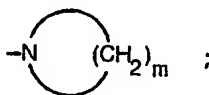
R_2 is hydrogen, alkyl
of from one to six carbon atoms,



R_3 is hydrogen or methyl;

R_4 is hydrogen or methyl;

or R_1 and R_2 taken together with the nitrogen atom to which they are attached form a ring denoted by



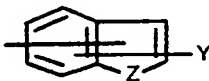
m is an integer of from three to eight;

n is zero or an integer of from one to six;

X is oxygen, sulphur, $-\text{CHR}_5$, or NR_5 ;

R_5 is hydrogen, alkyl of from one to six carbon atoms, or aryl;

R₆ is hydrogen or alkyl of from one to six carbon atoms;
A is



5

Y is hydrogen, fluorine, chlorine, alkyl or alkylene of from one to six carbon atoms, or aryl;
Z is oxygen, sulphur, —CH₂—, or NR₇; and R₇ is hydrogen, alkyl of from one to six carbon atoms, aryl,
or acyl of from 2 to 6 carbon atoms, or, when X is CHR₈, R₇ is the direct bond to X;
or an N¹-oxide of the compound of the foregoing structural formula; or
a pharmaceutically acceptable acid addition salt of the compound of the foregoing structural formula
or its N¹-oxide.

2. A compound in accordance with Claim 1, wherein m is 4, 5 or 6; or a pharmaceutically acceptable acid addition salt thereof.

3. A compound in accordance with Claim 1, wherein n is 0, 1 or 2; or a pharmaceutically acceptable acid addition salt thereof.

4. A compound in accordance with Claim 1, selected from the N¹-oxides of compounds of structural formula I; and pharmaceutically acceptable acid addition salts thereof.

5. A compound in accordance with Claim 4 having the name *trans*-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N¹-oxide-benzo[b]-thiophene-4-acetamide.

6. A compound in accordance with Claim 1, wherein Z is oxygen, the compound being selected from:
trans-N-2,4-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofuranacetamide;
trans-N-methyl-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacetamide;
and the pharmaceutically acceptable acid addition salts thereof.

7. A compound in accordance with Claim 1, wherein Z is sulphur, the compound being selected from:
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-N-methyl-N-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-[methyl(2-propenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-N-methylbenzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[methyl(2-propynyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-7-propyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thienyl)benzo[b]thiophene-7-acetamide;
trans-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-5-acetamide;
trans-N-methyl-N-[2-(1-piperidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-[methyl[(tetrahydro-2-furanyl)methyl]amino]cyclohexyl]benzo[b]thiophene-4-

acetamide;
trans-N-methyl-N-[2-methyl(3-methyl-2-butenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-[2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl]-N-methylbenzo[b]thiophene-4-

acetamide;
trans-N,5-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-N-methyl-N-[2-[methyl(3-methyl-2-butenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-[2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl]-N-methylbenzo[b]thiophene-4-

acetamide;
trans-N,5-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-5-chloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-N-methyl-N-[2-pyrrolidinylcyclohexyl]-4-benzo[b]thiophene-2-propionamide;
trans-2-(benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;
and the pharmaceutically acceptable addition salts thereof.

8. A compound in accordance with Claim 1, wherein X is CH₂, the compound being selected from:
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-2-acetamide;
and the pharmaceutically acceptable acid addition salts thereof.

9. A compound in accordance with Claim 1, wherein X is NR₇, where R₇ is as defined in Claim 1, the compound being selected from:

trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-propanamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-butanamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-1-acetamide;
trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N,2,3-trimethyl-1*H*-indole-5-acetamide;
trans-2,3,4,9-tetrahydro-N,9-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-carbazole-6-acetamide;

and the pharmaceutically acceptable acid addition salts thereof.

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13. A process for producing a compound in accordance with Claim 12, the process comprising reacting a compound of the formula



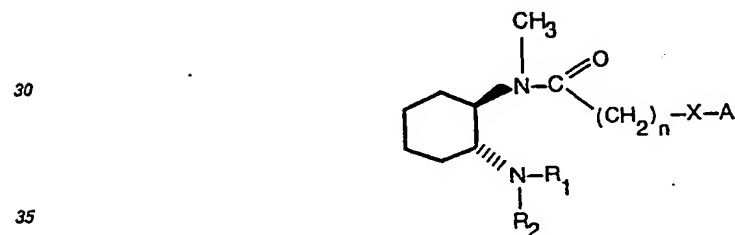
15 wherein R_1 and R_2 are as defined in Claim 12, with a carboxylic acid having the formula



wherein n , X , Y and Z are as defined in Claim 12, or with a reactive carboxylic derivative of said acid.

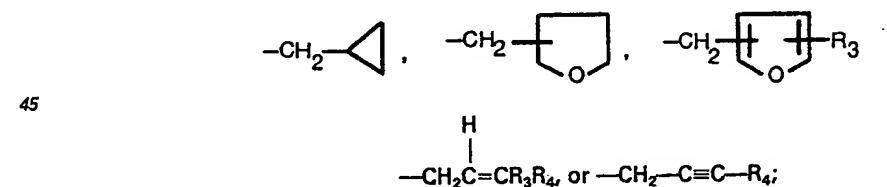
Claims for the Contracting State: AT

25 1. A process for producing a compound having the structural formula



where:

R_1 is methyl;
 R_2 is hydrogen, alkyl
 40 of from one to six carbon atoms,



R_3 is hydrogen or methyl;
 R_4 is hydrogen or methyl;
 or R_1 and R_2 taken together with the nitrogen atom to which they are attached form a ring denoted by



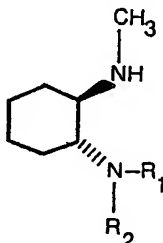
m is an integer of from three to eight;
 n is zero or an integer of from one to six;
 X is oxygen, sulphur, $-CHR_5$, or NR_6 ;
 R_5 is hydrogen, alkyl of from one to six carbon atoms, or aryl;
 R_6 is hydrogen or alkyl of from one to six carbon atoms;
 A is



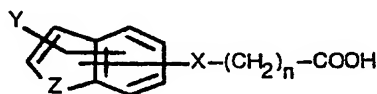
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Y is hydrogen, fluorine, chlorine, alkyl or alkylene of from one to six carbon atoms, or aryl;
Z is oxygen, sulphur, $-\text{CH}_2-$, or NR_7 ; and R_7 is hydrogen, alkyl of from one to six carbon atoms, aryl,
or acyl of from 2 to 6 carbon atoms, or, when X is CHR_6 , R_7 is the direct bond to X;
or an N^1 -oxide of the compound of the foregoing structural formula; or
a pharmaceutically acceptable acid addition salt of the compound of the foregoing structural formula
or its N^1 -oxide;

which process comprises reacting a compound of the formula



wherein R_1 and R_2 are as defined above, with a carboxylic acid having the formula



wherein n, X, Y, and Z are as defined above, or with a reactive carboxylic derivative of said acid: if necessary converting the compound to its N^1 -oxide; and if necessary converting the compound to an acid addition salt.

2. A process in accordance with Claim 1, wherein m is 4, 5 or 6; or a pharmaceutically acceptable acid addition salt thereof.

3. A process in accordance with Claim 1, wherein n is 0, 1 or 2; or a pharmaceutically acceptable acid addition salt thereof.

4. A process in accordance with Claim 1, for producing the N^1 -oxides of compounds of structural formula I; and pharmaceutically acceptable acid addition salts thereof.

5. A process in accordance with Claim 4 for producing *trans*-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]- N^1 -oxide-benzo[b]-thiophene-4-acetamide.

6. A process in accordance with Claim 1, wherein Z is oxygen, for producing a compound selected from:

trans-N-2,-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofuranacetamide;

trans-N-methyl-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacetamide; ...

and the pharmaceutically acceptable acid addition salts thereof.

7. A process in accordance with Claim 1, wherein Z is sulphur, for producing a compound selected from:

trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;

trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;

trans-N-methyl-N-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide;

trans-N-methyl-N-[2-[methyl(2-propenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;

trans-N-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-N-methylbenzo[b]thiophene-4-acetamide;

trans-N-methyl-N-[2-[methyl(2-propynyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;

trans-N-methyl-7-propyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;

trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thienyl)benzo[b]thiophene-7-acetamide;

trans-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-5-acetamide;

trans-N-methyl-N-[2-(1-piperidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;

trans-N-methyl-N-[2-[methyl[(tetrahydro-2-furanyl)methyl]amino]cyclohexyl]benzo[b]thiophene-4-acetamide;

trans-N-methyl-N-[2-methyl(3-methyl-2-butenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;

trans-N-[2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl]-N-methylbenzo[b]thiophene-4-acetamide;

trans-N,5-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;

trans-5-chloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;

trans-N-methyl-N-[2-pyrrolidinylcyclohexyl]-4-benzo[b]thiophene-2-propionamide;

trans-2-(benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

and the pharmaceutically acceptable addition salts thereof.

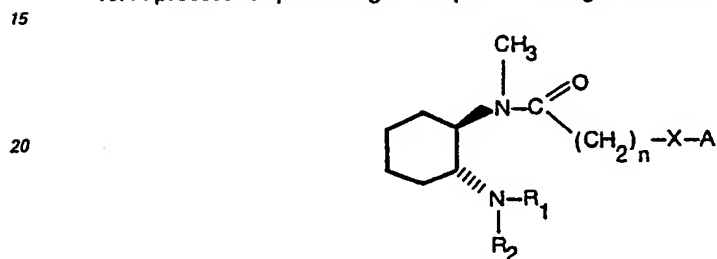
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8. A process in accordance with Claim 1, wherein X is CH₂, for producing a compound selected from:
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-2-acetamide;
 and the pharmaceutically acceptable acid addition salts thereof.

5 9. A process in accordance with Claim 1, wherein X is NR₇, where R₇ is as defined in Claim 1, for producing a compound selected from:

trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-propanamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-butanamide;
 10 *trans*-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-1-acetamide;
trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N,2,3-trimethyl-1*H*-indole-5-acetamide;
trans-2,3,4,9-tetrahydro-N,9-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-carbazole-6-acetamide;
 and the pharmaceutically acceptable acid addition salts thereof.

10. A process for producing a compound having the structural formula



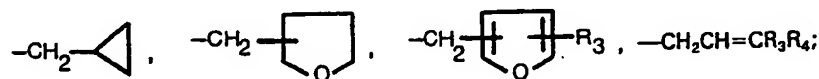
25 where:

R₁ is methyl;

R₂ is hydrogen, alkyl

of from one to six carbon atoms,

30



35 R₃ is hydrogen or methyl;

R₄ is hydrogen or methyl;

or R₁ and R₂ taken together with the nitrogen atom to which they are attached form a 5- or 6-membered

ring;

n is zero or an integer of from one to six;

40 X is oxygen, sulphur, —CHR₅ or NR₆;

R₅ is hydrogen, alkyl of from one to six carbon atoms, or aryl;

R₆ is hydrogen or alkyl of from one to six carbon atoms;

A is

45

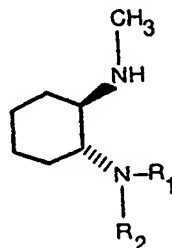


Y is hydrogen, fluorine, chlorine, alkyl of from one to six carbon atoms, or aryl;

Z is oxygen, sulphur, —CH₂—, or NR₇; and

50 R₇ is hydrogen, alkyl of from one to six carbon atoms, aryl, or acyl of from 2 to 6 carbon atoms; or
 a pharmaceutically acceptable acid addition salt of the compound of the foregoing structural formula:
 the process comprising reacting a compound of the formula

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wherein R_1 and R_2 are as defined above, with a carboxylic acid having the formula



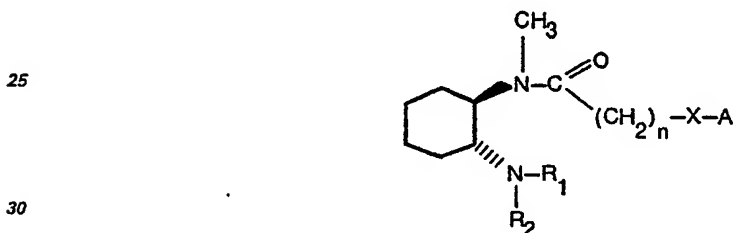
10 wherein n , X , Y and Z are as defined above, or with a reactive carboxylic derivative of said acid.

11. A process for producing a pharmaceutical composition, which comprises admixing a compound as produced in accordance with Claim 1, with a pharmaceutically acceptable carrier or diluent.

15

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

20 1. Verbindung der Strukturformel

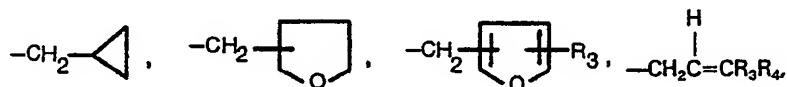


worin:

R_1 Methyl ist;

R_2 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen,

35



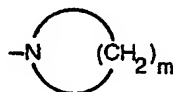
oder $-\text{CH}_2-\text{C}\equiv\text{C}-\text{R}_4$ steht;

R_3 für Wasserstoff oder Methyl steht;

R_4 für Wasserstoff oder Methyl steht; oder

R_1 und R_2 , wenn sie mit dem Stickstoffatom, an welches sie gebunden sind, zusammengenommen werden, einen Ring, gekennzeichnet

45



50 bilden;

m eine ganze Zahl von 3 bis 8 ist;

n für Null oder eine ganze Zahl von 1 bis 6 steht;

X für Sauerstoff, Schwefel, $-\text{CHR}_5$ oder NR_6 steht;

R_5 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;

55

R_6 für Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen steht;

A ist:

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Y für Wasserstoff, Fluor, Chlor, Alkyl oder Alkylen mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;

Z für Sauerstoff, Schwefel, $-\text{CH}_2-$ oder NR_7 steht; und worin

R Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Aryl oder Acyl mit 2 bis 6 Kohlenstoffatomen ist

65 oder wenn X für CHR_5 steht, R_7 die direkte Bindung an X bedeutet;

oder ein N¹-Oxid der Verbindung der oben stehenden Strukturformel;
oder ein pharmazeutisch akzeptables Säureadditionssalz der Verbindung der oben stehenden Strukturformel oder sein N¹-Oxid.

2. Verbindung nach Anspruch 1, worin m für 4, 5 oder 6 steht; oder ein pharmazeutisch akzeptables Säureadditionssalz davon.

3. Verbindung nach Anspruch 1, worin n für 0, 1 oder 2 steht; oder ein pharmazeutisch akzeptables Säureadditionssalz davon.

4. Verbindung nach Anspruch 1, ausgewählt aus den N¹-Oxiden der Verbindungen der Strukturformel I; und pharmazeutisch akzeptable Säureadditionssalze davon.

5. Verbindung nach Anspruch 4 mit dem Namen *trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N¹-oxid-benzo[b]-thiophen-4-acetamid.

6. Verbindung nach Anspruch 1, worin Z für Sauerstoff steht, wobei die Verbindung ausgewählt ist aus:

trans-N-2,-Dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-3-benzofuranacetamid;
trans-N-Methyl-phenyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-5-benzofuranacetamid;
und die pharmazeutisch akzeptablen Säureadditionssalze davon.

7. Verbindung nach Anspruch 1, worin Z für Schwefel steht, wobei die Verbindung ausgewählt ist aus:

trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-3-acetamid;
trans-N-Methyl-N-[2-(methylamino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(methyl-(2-propenyl)-amino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-[2-[(Cyclopropylmethyl)-methylamino]-cyclohexyl]-N-methylbenzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(methyl-(2-propenyl)-amino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-7-propyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-3-(2-thienyl)-benzo[b]-thiophen-7-acetamid;
trans-N-Methyl-3-phenyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-5-acetamid;
trans-N-Methyl-N-[2-(1-piperidinyl)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(methyl-[(tetrahydro-2-furanyl)-methyl]-amino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-methyl-(3-methyl-2-butenyl)amino]-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-[2-[(1,1-Dimethyl-2-propenyl)-methylamino]-cyclohexyl]-N-methylbenzo[b]thiophen-4-acetamid;

trans-N,5-Dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[b]-thiophen-3-acetamid;
trans-N-Methyl-N-[2-(Methyl-(3-methyl-2-butenyl)-amino)-cyclohexyl]benzo[b]-thiophen-4-acetamid;
trans-N-[2-[(1,1-Dimethyl-2-propenyl)-methylamino]-cyclohexyl]-N-methylbenzo[b]-thiophen-4-acetamid;

trans-N,5-Dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[b]-thiophen-3-acetamid;
trans-5-Chlor-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[b]-thiophen-3-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-4-benzo[b]thiophen-2-propionamid;
trans-2-(Benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-acetamid;

und die pharmazeutisch akzeptablen Säureadditionssalze davon.

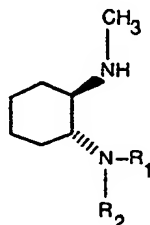
8. Verbindung nach Anspruch 1, worin X für CH₂ steht, wobei die Verbindung ausgewählt ist aus:
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-inden-3-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-inden-2-acetamid;

und die pharmazeutisch akzeptablen Säureadditionssalze davon.

9. Verbindung nach Anspruch 1, worin X für NR₇ steht, worin R₇ wie im Anspruch 1 definiert ist, wobei die Verbindung ausgewählt ist aus:
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-propanamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-butanamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-1-acetamid;
trans-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N,2,3-trimethyl-1*H*-indol-5-acetamid;
trans-2,3,4,9-Tetrahydro-N,9-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-carbazol-6-acetamid;

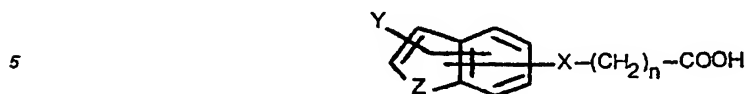
und die pharmazeutisch akzeptablen Säureadditionssalze davon.

10. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, welches Verfahren umfaßt: die Umsetzung einer Verbindung der Formel



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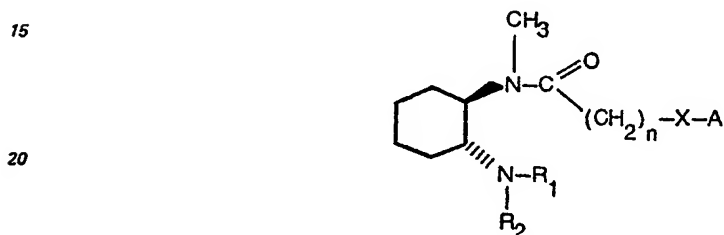
worin R_1 und R_2 wie in Anspruch 1 definiert sind, mit einer Carbonsäure der Formel



worin n , X , Y und Z wie in Anspruch 1 definiert sind, oder mit einem reaktiven Carbonsäure-Derivat dieser Säure.

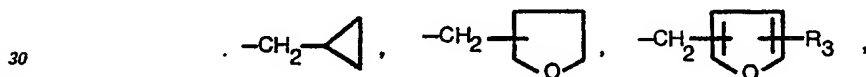
10 11. Pharmazeutische Zusammensetzung, welche zur Linderung von Schmerz bei einem Säuger nützlich ist, welche Zusammensetzung eine wirksame Menge einer Verbindung nach Anspruch 1 in Kombination mit einem pharmazeutisch akzeptablen Träger umfaßt.

12. Verbindung der Strukturformel



worin

25 R_1 für Methyl steht;
 R_2 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen,



— $CH_2CH=CR_3R_4$ ist;

35 R_3 für Wasserstoff oder Methyl steht;
 R_4 für Wasserstoff oder Methyl steht; oder
 R_1 und R_2 , wenn sie mit dem Stickstoffatom, an welches sie gebunden sind, zusammengekommen werden, einen 5- oder 6-gliedrigen Ring bilden;
 n für Null oder eine ganze Zahl von 1 bis 6 steht;
 X Sauerstoff, Schwefel, — CHR_5 oder NR_6 ist;
 R_5 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;
 R_6 Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen ist;
 A ist:



Y für Wasserstoff, Fluor, Chlor, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;

Z Sauerstoff, Schwefel, — CH_2 — oder NR_7 ist; und

R_7 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Aryl oder Acyl mit 2 bis 6 Kohlenstoffatomen steht; oder

50 ein pharmazeutisch akzeptables Säureadditionssalz der Verbindung der obigen Strukturformel.

13. Verfahren zur Herstellung einer Verbindung nach Anspruch 12, welches Verfahren umfaßt: die Umsetzung einer Verbindung der Formel



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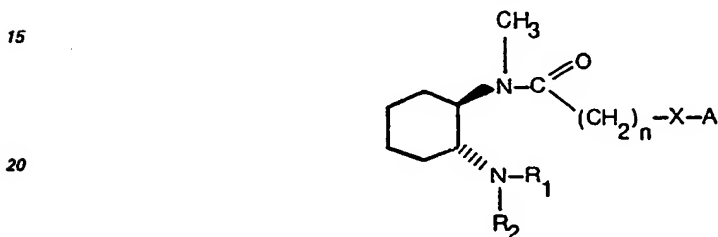
worin R_1 und R_2 wie im Anspruch 12 definiert sind, mit einer Carbonsäure der Formel



worin n , X , Y und Z wie im Anspruch 12 definiert sind, oder mit einem reaktiven carboxylishem Derivat dieser Säure.

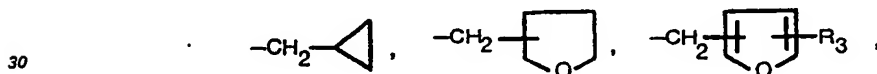
10 Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Strukturformel



worin:

- 25 R_1 für Methyl steht;
 R_2 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen,



oder $-\text{CH}_2-\text{C}\equiv\text{C}-\text{R}_4$ steht;

- 35 R_3 Wasserstoff oder Methyl ist;
 R_4 für Wasserstoff oder Methyl steht; oder
 R_1 und R_2 , wenn sie mit dem Stickstoffatom, an welches sie gebunden sind, zusammengenommen werden, einen Ring, gekennzeichnet



bilden;

- 45 m eine ganze Zahl von 3 bis 8 ist;
 n für Null oder eine ganze Zahl von 1 bis 6 steht;
 X für Sauerstoff, Schwefel, $-\text{CHR}_5$ oder NR_6 steht;
 R_5 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl ist;
 R_6 für Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen steht;
 A für:



- 55 Y für Wasserstoff, Fluor, Chlor, Alkyl oder Alkylen mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;
 Z für Sauerstoff, Schwefel, $-\text{CH}_2-$ oder NR_7 steht; und
 R_7 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Aryl oder Acyl mit 2 bis 6 Kohlenstoffatomen ist
oder wenn X für CHR_5 steht, R_7 die direkte Bindung an X bedeutet;
oder eines N^1 -Oxids der Verbindung der oben stehenden Strukturformel;
60 oder eines pharmazeutisch akzeptablen Säureadditionssalzes der Verbindung der oben stehenden Strukturformel oder ihres N^1 -Oxids;
welches Verfahren umfaßt:

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die Umsetzung einer Verbindung der Formel



15 worin R₁ und R₂ wie oben definiert sind, mit einer Carbonsäure der Formel



25 worin n, X, Y und Z wie oben definiert sind, oder mit einem reaktiven carboxylischem Derivat dieser Säure; falls erforderlich Überführen der Verbindung in ihr N¹-Oxid; und falls erforderlich Überführen der Verbindung in ein Säureadditionssalz.

2. Verfahren nach Anspruch 1, worin m für 4, 5 oder 6 steht; oder ein pharmazeutisch akzeptables Säureadditionssalz davon.

3. Verfahren nach Anspruch 1, worin n für 0, 1 oder 2 steht; oder ein pharmazeutisch akzeptables Säureadditionssalz davon.

4. Verfahren nach Anspruch 1, zur Herstellung der N¹-Oxide der Verbindungen der Strukturformel I; und pharmazeutisch akzeptablen Säureadditionssalze davon.

5. Verfahren nach Anspruch 4 zur Herstellung von *trans*-N-Methyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-N¹-oxid-benzo[b]-thiophen-4-acetamid.

6. Verfahren nach Anspruch 1, worin Z Sauerstoff ist, zur Herstellung einer Verbindung, welche ausgewählt ist aus:

trans-N-2-Dimethyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-3-benzofuranacetamid;

35 *trans*-N-Methyl-phenyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-5-benzofuranacetamid; und der pharmazeutisch akzeptablen Säureadditionssalze davon.

7. Verfahren nach Anspruch 1, worin Z Schwefel ist, zur Herstellung einer Verbindung ausgewählt aus:

trans-N-Methyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-benzo[b]-thiophen-3-acetamid;

40 *trans*-N-Methyl-N-[2-(methylamino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-[methyl-(2-propenyl)-amino]-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

... *trans*-N-[2-[(Cyclopropylmethyl)-methylamino]-cyclohexyl]-N-methylbenzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-[methyl-(2-propenyl)-amino]-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-7-propyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

45 *trans*-N-Methyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-3-(2-thienyl)-benzo[b]-thiophen-7-acetamid;

trans-N-Methyl-3-phenyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-benzo[b]-thiophen-5-acetamid;

trans-N-Methyl-N-[2-(1-piperidiny)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-[methyl-[(tetrahydro-2-furanyl)-methyl]-amino]-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

50 *trans*-N-Methyl-N-[2-methyl-(3-methyl-2-butenyl)amino]-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-[2-[(1,1-Dimethyl-2-propenyl)-methylamino]-cyclohexyl]-N-methylbenzo[b]thiophen-4-acetamid;

trans-N,5-Dimethyl-N-[2-(1-pyrrolidiny)-cyclohexyl]benzo[b]-thiophen-3-acetamid;

trans-N-Methyl-N-[2-[methyl-(3-methyl-2-butenyl)-amino]-cyclohexyl]benzo[b]-thiophen-4-acetamid;

55 *trans*-N-[2-[(1,1-Dimethyl-2-propenyl)-methylamino]-cyclohexyl]-N-methylbenzo[b]-thiophen-4-acetamid;

trans-N,5-Dimethyl-N-[2-(1-pyrrolidiny)-cyclohexyl]benzo[b]-thiophen-3-acetamid;

trans-5-Chlor-N-methyl-N-[2-(1-pyrrolidiny)-cyclohexyl]benzo[b]-thiophen-3-acetamid;

trans-N-Methyl-N-[2-pyrrolidiny]cyclohexyl]-4-benzo[b]thiophen-2-propionamid;

60 *trans*-2-(Benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-acetamid; und der pharmazeutisch akzeptablen Additionsalze davon.

8. Verfahren nach Anspruch 1, worin X für CH₂ steht, zur Herstellung einer Verbindung ausgewählt aus:

trans-N-Methyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-1*H*-inden-3-acetamid;

trans-N-Methyl-N-[2-(1-pyrrolidiny)-cyclohexyl]-1*H*-inden-2-acetamid;

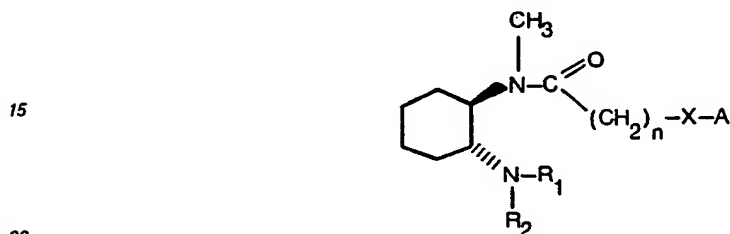
65 und der pharmazeutisch akzeptablen Säureadditionssalze davon.

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9. Verfahren nach Anspruch 1, worin X für NR₇ steht, worin R₇ wie im Anspruch 1 definiert ist, zur Herstellung einer Verbindung welche ausgewählt ist aus:

- trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-acetamid;
 - trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-propanamid;
 - trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-butanamid;
 - trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-1-acetamid;
 - trans*-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N,2,3-trimethyl-1*H*-indol-5-acetamid;
 - trans*-2,3,4,9-Tetrahydro-N,9-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-carbazol-6-acetamid;
- und der pharmazeutisch akzeptablen Säureadditionssalze davon.

10. Verfahren zur Herstellung einer Verbindung der Strukturformel



worin

- R₁ für Methyl steht;
- R₂ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen,

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—CH₂CH=CR₃R₄ ist;

- R₃ für Wasserstoff oder Methyl steht;
- R₄ für Wasserstoff oder Methyl steht; oder
- R₁ und R₂, wenn sie mit dem Stickstoffatom, an welches sie gebunden sind, zusammengenommen werden, einen 5- oder 6-gliedrigen Ring bilden;
- n für Null oder eine ganze Zahl von 1 bis 6 steht;
- X für Sauerstoff, Schwefel, —CHR₅ oder NR₆ steht;
- R₅ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl ist;
- R₆ Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen ist;
- A ist:

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Y für Wasserstoff, Fluor, Chlor, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;

Z Sauerstoff, Schwefel, —CH₂— oder NR₇ ist; und

R₇ für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Aryl oder Acyl mit 2 bis 6 Kohlenstoffatomen

steht; oder

eines pharmazeutisch akzeptablen Säureadditionssalzes der Verbindung der oben stehenden

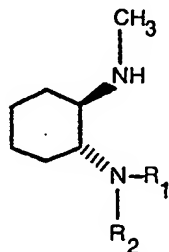
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Strukturformel;

welches Verfahren umfaßt:

die Umsetzung einer Verbindung der Formel

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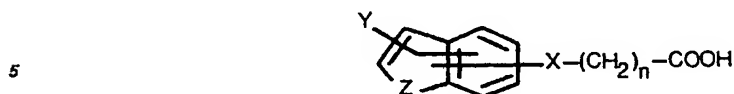


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worin R_1 und R_2 wie oben definiert sind, mit einer Carbonsäure der Formel

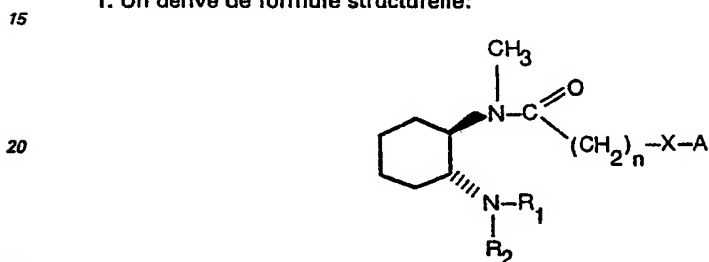


worin n , X , Y und Z wie oben definiert sind, oder mit einem reaktiven carboxylischem Derivat dieser Säure.

11. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welches das Mischen einer nach Anspruch 1 hergestellten Verbindung mit einem pharmazeutisch akzeptablen Träger oder Verdünnungsmittel umfaßt.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

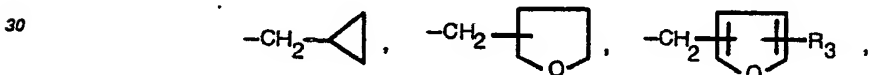
1. Un dérivé de formule structurelle:



dans laquelle:

R_1 représente le radical méthyle; et

R_2 représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone,



$-\text{CH}_2\text{CH}=\text{CR}_3\text{R}_4$ ou $-\text{CH}_2-\text{C}\equiv\text{C}-\text{R}_4$, R_3 et R_4 représentant indépendamment un atome d'hydrogène ou un radical méthyle; ou dans laquelle

35 R_1 et R_2 , pris ensemble en même temps que l'atome d'azote auquel ils sont attachés, forment un cycle répondant au schéma:



dans lequel

m est un nombre entier de 3 à 8;

n est un entier de 0 à 6;

45 X représente un atome d'oxygène, de soufre ou CHR_5 , dans lequel R_5 représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

ou X représente NR_6 , R_6 étant un atome d'hydrogène ou un radical alkyle renfermant de 1 à 6 atomes de carbone;

A représentant:



où:

55 Y représente un atome d'hydrogène, de fluor, de chlore, un radical alkyle ou alkylène renfermant de 1 à 6 atomes de carbone ou un radical aryle; et

Z représente un atome d'oxygène, de soufre, $-\text{CH}_2-$ ou NR_7 , R_7 étant un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone, aryle ou acyle renfermant de 2 à 6 atomes de carbone

60 où, lorsque X représente CHR_5 , R_7 représente la liaison directe avec X ; ou un N¹-oxyde du dérivé de formule structurelle suivante; ou un sel d'addition d'acide pharmaceutiquement acceptable du dérivé de formule structurelle ci-dessus ou de son N¹-oxyde.

2. Un dérivé selon la revendication 1, dans lequel m est égal à 4, 5 ou 6 ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

65 3. Un dérivé selon la revendication 1, dans lequel n est égal à 0, 1 ou 2, ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

4. Un dérivé selon la revendication 1, choisi parmi les N¹-oxydes des dérivés de formule structurelle I, et leurs sels d'addition d'acides pharmaceutiquement acceptables.

5. Un dérivé selon la revendication 4, désigné sous le nom de: trans-N-méthyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N¹-oxyde-benzo[b]thiophène-4-acétamide.

6. Un dérivé selon la revendication 1, dans lequel Z représente un atome d'oxygène, le dérivé étant choisi parmi les suivants:

trans-N-2-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofurmacétamide;
trans-N-méthyl-phényl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacétamide;

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

7. Un dérivé selon la revendication 1, dans lequel Z représente le soufre, le dérivé étant choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;
trans-N-méthyl-N-[2-(méthylamino)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-(méthyl-(2-propényl)amino)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-[2-[(cyclopropylméthyl)méthylamino]cyclohexyl]-N-méthylbenzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-(méthyl-(2-propényl)amino)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-7-propyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thiényl)benzo[b]thiophène-7-acétamide;
trans-N-méthyl-3-phényl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-5-acétamide;
trans-N-méthyl-N-[2-(1-pipéridinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-méthyl[(tétrahydro-2-furanyl)méthyl]amino]cyclohexyl]benzo[b]thiophène-4-

acétamide;

trans-N-méthyl-N-[2-méthyl-(3-méthyl-2-butényl)-amino-cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-[2-[(1,1-diméthyl-2-propényl)méthylamino]cyclohexyl]-N-méthylbenzo[b]thiophène-4-

acétamide;

trans-N-5-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;
trans-N-méthyl-N-[2-(méthyl(3-méthyl-2-butényl)amino)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-[2-[(1,1-diméthyl-2-propényl)méthylamino]cyclohexyl]-N-méthylbenzo[b]thiophène-4-

acétamide;

trans-N-5-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;
trans-5-chloro-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[b]thiophène-2-propionamide;
trans-2-(benzo[b]thiophène-3-yloxy)-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acétamide;

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

8. Un dérivé selon la revendication 1, dans lequel X représente CH₂, le dérivé étant choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indène-3-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indène-2-acétamide;

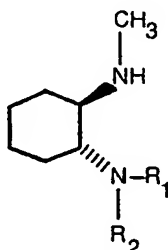
et leurs sels d'addition d'acides pharmaceutiquement acceptables.

9. Un dérivé selon la revendication 1, dans lequel X représente NR₇, R₇ étant tel que défini dans la revendication 1, le dérivé étant choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-propanamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-butanamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-1-acétamide;
trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N-2,3-triméthyl-1H-indole-5-acétamide;
trans-2,3,4,9-tétrahydro-N-9-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-carbazole-6-acétamide;

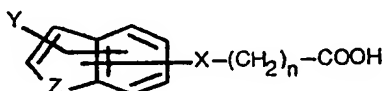
et leurs sels d'addition d'acides pharmaceutiquement acceptables.

10. Un procédé de préparation d'un dérivé en accord avec la revendication 1, ce procédé consistant à faire réagir un dérivé de formule:



dans laquelle:

R₁ et R₂ sont tels que définis dans la revendication 1; avec un acide carboxylique répondant à la formule:



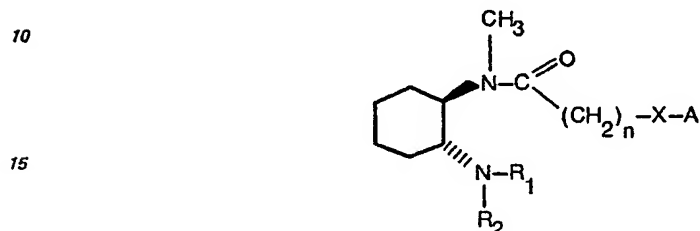
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dans laquelle:

n, X, Y et Z sont tels que définis dans la revendication 1, ou avec un dérivé carboxylique réactif de cet acide.

11. Une composition pharmaceutique utile pour soulager la douleur d'un mammifère, cette composition comprenant une quantité efficace d'un dérivé selon la revendication 1, en association avec un support pharmaceutiquement acceptable.

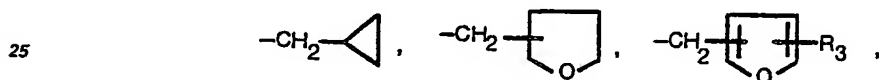
12. Un dérivé de formule structurelle:



dans laquelle:

20 R₁ représente le radical méthyle;

R₂ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone;



—CH₂CH=CR₃R₄ ou —CH₂—C≡C—R₄,

R₃ représente un atome d'hydrogène ou la radical méthyle;

30 R₄ représente un atome d'hydrogène ou le radical méthyle;

ou R₁ et R₂, pris ensemble en même temps que l'atome d'azote auquel ils sont attachés, forment un cycle à 5 ou 6 éléments;

n est égal à 0 ou un nombre entier de 1 à 6, bornes comprises;

X représente un atome d'oxygène, de soufre, CHR₅, ou NR₆,

35 R₅ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

R₆ représente un atome d'hydrogène ou un radical alkyle renfermant de 1 à 6 atomes de carbone;

A représente:



45 Y représente un atome d'hydrogène, de fluor, de chlore, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

Z représente un atome d'oxygène, de soufre, —CH₂— ou NR₇, R₇ étant un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone, aryle ou acyle renfermant de 2 à 6 atomes de carbone;

50 ou un sel d'addition d'acide pharmaceutiquement acceptable du dérivé répondant à la formule structurelle précédente.

13. Un procédé de préparation d'un dérivé selon la revendication 12, ce procédé consistant à faire réagir un dérivé de formule:



65 dans laquelle R₁ et R₂ sont tels que définis dans la revendication 12;

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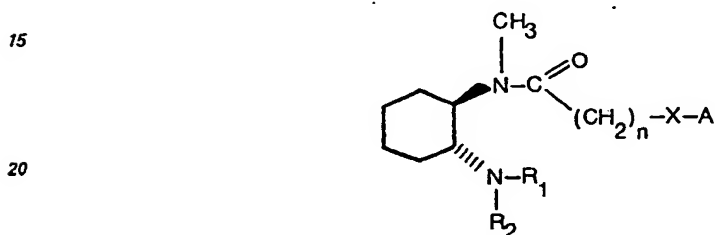
avec un acide carboxylique de formule:



dans laquelle n, X, Y et Z sont tels que définis dans la revendication 12, ou avec un dérivé carboxylique réactif de cet acide.

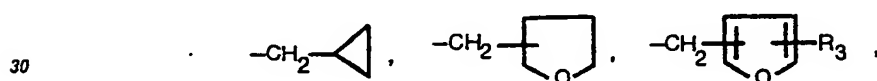
10 Revendications pour l'Etat contractant: AT

1. Un procédé de préparation d'un dérivé de formule structurelle:



dans laquelle:

25 R₁ représente le radical méthyle; et
R₂ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone,



—CH₂CH=CR₃R₄ ou —CH₂—C≡C—R₄, R₃ et R₄ représentant indépendamment un atome d'hydrogène ou un radical méthyle;

35 ou dans laquelle R₁ et R₂, pris ensemble en même temps que l'atome d'azote auquel ils sont attachés, forment un cycle répondant au schéma:



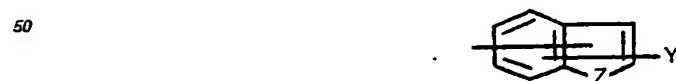
dans lequel m est un nombre entier de 3 à 8;

n est un entier de 0 à 6;

45 X représente un atome d'oxygène, de soufre ou CHR₅, dans lequel R₅ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

ou X représente NR₆, R₆ étant un atome d'hydrogène ou un radical alkyle renfermant de 1 à 6 atomes de carbone;

A représentant:



ou:

55 Y représente un atome d'hydrogène, de fluor, de chlore, un radical alkyle ou alkylène renfermant de 1 à 6 atomes de carbone ou un radical aryle; et

Z représente un atome d'oxygène, de soufre, —CH₂— ou NR₇, R₇ étant un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone, aryle ou acyle renfermant de 2 à 6 atomes de carbone où, lorsque X représente CHR₆, R₇ représente la liaison directe avec X;

60 ou un N¹-oxyde du dérivé de formule structurelle suivante; ou un sel d'addition d'acide pharma-

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ceutiquement acceptable du dérivé de formule structurelle ci-dessus ou de son N¹-oxyde; ce procédé consistant à faire réagir un dérivé de formule:



15 dans laquelle R₁ et R₂ sont tels que définis ci-dessus; avec un acide carboxylique de formule:



dans laquelle n, X, Y et Z sont tels que définis ci-dessus; ou avec un dérivé carboxylique réactif de cet acide et, si nécessaire, on convertit le dérivé en son N¹-oxyde et, si nécessaire, on convertit le dérivé en un sel d'addition d'acide.

2. Un procédé selon la revendication 1, dans lequel m est égal à 4, 5 ou 6 ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

3. Un procédé selon la revendication 1, dans lequel n est égal à 0, 1 ou 2, ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

4. Un procédé selon la revendication 1 de préparation des N¹-oxydes des dérivés de formule structurelle I, et leurs sels d'addition d'acides pharmaceutiquement acceptables.

5. Un procédé selon la revendication 4 de préparation de trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-N¹-oxyde-benzo[b]thiophène-4-acétamide.

6. Un procédé selon la revendication 1, dans lequel Z représente un atome d'oxygène, de préparation d'un dérivé choisi parmi:

trans-N-2-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofuranacétamide;

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacétamide;

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

7. Un procédé selon la revendication 1, dans lequel Z représente le soufre, de préparation d'un dérivé etant choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;

trans-N-méthyl-N-[2-(méthylamino)cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-(méthyl-(2-propényl)amino)cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-[2-((cyclopropylméthyl)méthylamino)cyclohexyl]-N-méthylbenzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-(méthyl-(2-propényl)amino)cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thiényl)benzo[b]thiophène-7-acétamide;

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-5-acétamide;

trans-N-méthyl-N-[2-(1-pipéridinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-méthyl-((tétrahydro-2-furanyl)méthyl)amino]cyclohexyl]benzo[b]thiophène-4-

acétamide;

trans-N-méthyl-N-[2-méthyl-(3-méthyl-2-butényl)-amino-cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-[2-((1,1-diméthyl-2-propényl)méthylamino)cyclohexyl]-N-méthylbenzo[b]thiophène-4-

acétamide;

trans-N-5-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;

trans-N-méthyl-N-[2-(méthyl(3-méthyl-2-butényl)amino)cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-[2-((1,1-diméthyl-2-propényl)méthylamino)cyclohexyl]-N-méthylbenzo[b]thiophène-4-

acétamide;

trans-N-5-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;

trans-5-chloro-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;

trans-2-(benzo[b]thiophène-3-yloxy)-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acétamide;

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

8. procédé dérivé selon la revendication 1, dans lequel X représente CH₂, de préparation d'un dérivé choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indène-3-acétamide;

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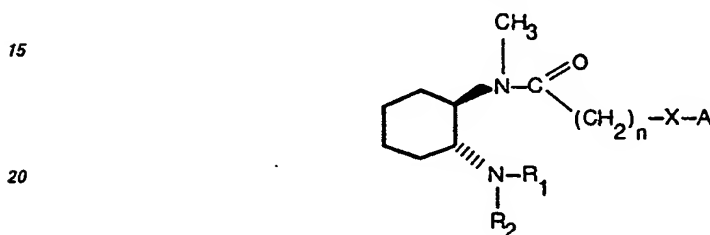
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indène-2-acétamide;
et leurs sels d'addition d'acides pharmaceutiquement acceptables.

9. Un procédé selon la revendication 1, dans lequel X représente NR₇, R₇ étant tel que défini dans la revendication 1, de préparation d'un dérivé choisi parmi:

- 5 trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-acétamide;
- trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-propanamide;
- trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-butanamide;
- trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-1-acétamide;
- 10 trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N-2,3-triméthyl-1H-indole-5-acétamide;
- trans-2,3,4,9-tétrahydro-N-9-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-carbazole-6-acétamide;

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

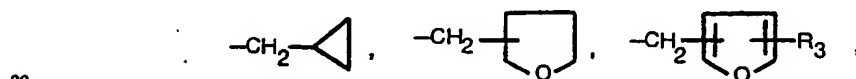
10. Un procédé de préparation d'un dérivé de formule structurelle:



dans laquelle:

25 R₁ représente le radical méthyle;

R₂ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone;



—CH₂CH=CR₃R₄ ou —CH₂—C≡C—R₄,

R₃ représente un atome d'hydrogène ou le radical méthyle;

R₄ représente un atome d'hydrogène ou le radical méthyle;

35 ou R₁ et R₂, pris ensemble en même temps que l'atome d'azote auquel ils sont attachés, forment un cycle à 5 ou 6 éléments;

n est égal à 0 ou un nombre entier de 1 à 6, bornes comprises;

X représente un atome d'oxygène, de soufre, CHR₅, ou NR₆,

40 R₅ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

R₆ représente un atome d'hydrogène ou un radical alkyle renfermant de 1 à 6 atomes de carbone;

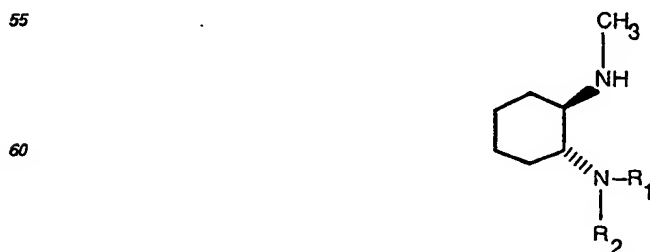
A représente:



Y représente un atome d'hydrogène, de fluor, de chlore, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

50 Z représente un atome d'oxygène, de soufre, —CH₂— ou NR₇, R₇ étant un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone, aryle ou acyle renfermant de 2 à 6 atomes de carbone;

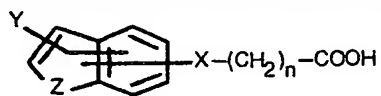
ou un sel d'addition d'acide pharmaceutiquement acceptable du dérivé répondant à la formule structurelle ci-dessus, ce procédé consistant à faire réagir un dérivé de formule:



65

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dans laquelle R_1 et R_2 sont tels que définis ci-dessus; avec un acide carboxylique de formule:



dans laquelle n, X, Y et Z sont tels que définis ci-dessus; ou avec un dérivé carboxylique réactif de cet acide.

11. Un procédé de préparation d'une composition pharmaceutique, qui consiste à mélanger un dérivé obtenu selon la revendication 1, avec un support ou diluant pharmaceutiquement acceptable.

(10)



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(54) **Substituted trans-1,2-diaminocyclohexyl amide compounds.**

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The file contains technical information
submitted after the application was filed and
not included in this specification

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Courier Press, Leamington Spa, England.

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Description

The search for strong analgesics which also possess minimal potential for dependency has been among the highest priority efforts in pharmacological research. These research efforts have, to a great extent, involved chemical modifications of the opiate structure and the discovery of chemically novel compounds which possess morphine-like activity.

The discovery of endogenous opioids has led workers in the field to consider that these peptides, possessing less rigid structures, might interact with opioid receptors other than those to which the classical rigid structure opiates, such as morphine, bind.

The concept of multiple opioid receptors has been supported by studies with nalorphine and a series of benzomorphans which display unusual pharmacological properties dissimilar from morphine, yet blocked by the selective opioid antagonists. [See, for example, W. R. Martin, et al., *J. Pharmacol. Exp. Ther.*, 197: 517—532 (1976)].

The existence of multiple types of opioid receptors is of importance because it suggests the possibility of separating the desirable analgesic and psychotherapeutic effects of a drug compound from the undesirable abuse potential or habituating effects.

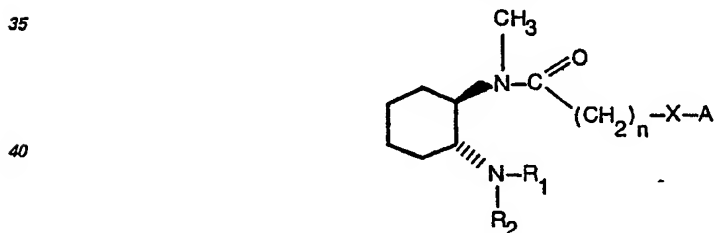
British Patent Application GB 2096607 and United States Patent 4,145,435 describe certain 2-amino-cycloaliphatic amide compounds as analgesics. In particular, *trans*-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]-benzacetamide has been reported to possess selective kappa agonist activity, and therefore to possess analgesic activity without attendant dependence liability. [See P.V. Vanvogtlander, et al., *J. Pharmacol. Exp. Ther.*, 224: 7—12 (1983)].

Recently, the diuretic effect of various opioid agonists and antagonists has been studied, and it has been shown that kappa agonists tend to increase urination, while mu agonists decreased urination. [See J. D. Leander, *J. Pharmacol. Exp. Ther.*, 227: 35—41 (1983)]. These findings suggest that selective opioid agonists and antagonists also possess potential as diuretics.

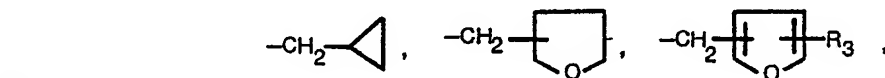
Summary of the Invention

The present invention relates to substituted *trans*-1,2-diamino-cyclohexylamide compounds useful as analgesics, diuretics, and psychotherapeutic agents. The invention is also concerned with a method of preparing such compounds, pharmaceutical compositions including such compounds, and with their use in alleviating pain in a mammal by administering an effective amount of a pharmaceutical composition in accordance with the present invention.

In its broadest aspect, the present invention encompasses compounds having structural formula I



wherein R_1 is methyl and R_2 is hydrogen, alkyl of from one to six carbon atoms



— $\text{CH}_2\text{CH}=\text{CR}_3\text{R}_4$ or — $\text{CH}_2\text{C}\equiv\text{C—R}_4$ where R_3 and R_4 are independently hydrogen or methyl; or where R_1 and R_2 taken together with the nitrogen atom to which they are attached form a ring denoted by



where m is an integer of from three to eight; where n is an integer of from zero to six; X is oxygen, sulfur, or CHR_5 , where R_5 is hydrogen, alkyl of from one to six carbon atoms, or aryl; or X is NR_6 where R_6 is hydrogen or alkyl of from one to six carbon atoms; where A is



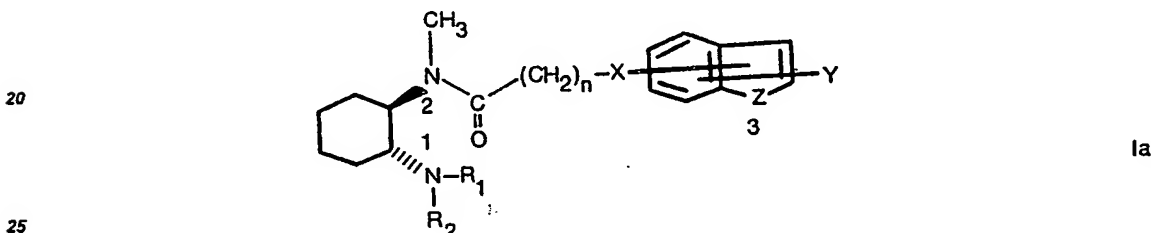
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where Y is hydrogen, fluorine, chlorine, alkyl or alkylene of from one to six carbon atoms, or aryl; and Z is oxygen, sulfur, $-\text{CH}_2-$, or NR_7 , where R_7 is hydrogen, alkyl of from one to six carbon atoms, aryl or acryl of one to six carbon atoms, or, when X is CHR_5 , R_7 is the direct bond to X; or N¹-oxides thereof; and the pharmaceutically acceptable acid addition salts thereof.

5 In structural formula IIIb for subunit "A" above, the bond shown attaching the group "Y" to the fused ring system is drawn to intersect both rings of the fused ring system. This notation is meant to indicate that Y may be attached to the fused ring system at positions 2, 3, 4, 5, 6, and 7.

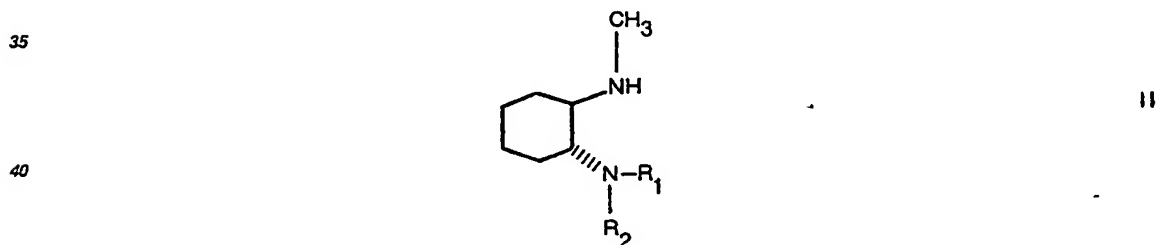
Likewise, the position of attachment of the group designated "X" to the fused ring system designated "A" may be at positions 2, 3, 4, 5, 6, or 7. Moreover, when Z is a nitrogen atom and X is CHR_5 , the nitrogen atom of the heterocyclic fused ring system may be attached by a direct bond to X.

10 Also contemplated as falling within this aspect of the present invention are the N¹-oxides of compounds having structural formula I above. The meaning of the term "N¹-oxides" is made clear by referring to structural formula Ia below in which the nitrogen atoms have been numbered. The alkyl-substituted nitrogen atom is numbered "1" and the amido-nitrogen atom is numbered "2." In these cases
15 where Z is also nitrogen, this is numbered nitrogen atom "3."

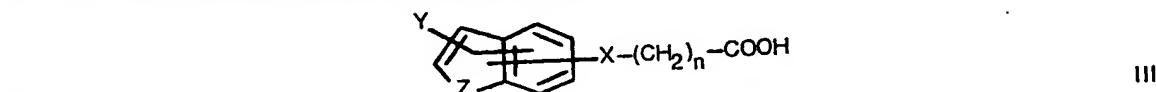


Oxidation of compounds of structural formula I above with, for example, m-chloroperbenzoic acid or other suitable oxidizing agents, readily converts the more basic alkyl-substituted nitrogen atom attached to the cyclohexane ring to its corresponding N-oxide. Throughout this specification and the appended claims, the term "N¹-oxide" is meant to refer to these compounds.

30 In accordance with a second aspect of the present invention, a method of preparing compounds having structural formula I comprises reacting a substituted *trans*-cyclohexyldiamine of structure II



45 with a substituted carboxylic acid of structural formula III.



In accordance with another aspect of the present invention, pharmaceutical compositions useful for the alleviation of pain in a mammal comprise an effective amount of compound having structural formula I above, in combination with a pharmaceutically acceptable carrier.

55 In a further aspect of the present invention, we provide compounds of formula I above for use in a method of alleviating pain in a mammal which method comprises administering to a mammal suffering from pain an effective amount of a pharmaceutical composition, preferably in unit dosage form, which composition includes a compound having structural formula I, above, in combination with a pharmaceutically acceptable carrier.

Detailed Description

60 Compounds of the present invention comprise a class of derivatives of *trans*-1,2-diaminocyclohexane in which nitrogen is a tertiary amine nitrogen substituted with methyl and a substituent selected from the group R_2 as defined above or, preferably is a tertiary amine nitrogen attached to the cyclohexane ring and which preferably is part of a pyrrolidinyl, piperidinyl or homopiperidinyl group. The other nitrogen atom of
65 the 1,2-diaminocyclohexane is an N-methyl amide nitrogen.

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In the formula for the subunit designated "A" above, the bonds shown attaching the groups "X" and "Y" to the fused ring system are drawn to intersect both the carbocyclic and the heterocyclic rings of the fused ring system. This notation is meant to indicate that X and Y may be attached to the fused ring system at positions 2, 3, 4, 5, 6, or 7. Moreover, when Z is nitrogen, X may be attached to position 1. In those cases where Y is hydrogen, alkyl, or aryl, Y may likewise be attached to position 1 when X is attached at a position 2 through 7.

By the term "alkyl of from one to six carbon atoms" as used throughout this specification and the appended claims is meant branched or unbranched saturated hydrocarbon groupings containing one to six carbon atoms. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, n-pentyl, and the like.

By the term "aryl" is meant phenyl; phenyl substituted with fluorine, chlorine, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, nitro, and trifluoromethyl; thienyl; and thienyl substituted with alkyl of from one to six carbon atoms, and alkoxy of from one to six carbon atoms.

By the term "alkoxy" is meant a branched or unbranched hydrocarbon grouping such as "alkyl" as defined above, attached to an oxygen atom.

By the term "acyl" as used herein is meant an organic radical derived from an organic acid by the removal of the hydroxy group, for example, acetyl, benzoyl, methanesulfonyl, benzenesulfonyl, p-toluenesulfonyl and the like. Thus, the term is meant to encompass alkanoyl and alkanesulfonyl where the alkyl portion is "alkyl" as defined above; aroyl and arylsulfonyl where the aromatic portion is "aryl" as defined above.

Compounds of the present invention may contain one or more asymmetric carbon atoms and thus exist as enantiomers or diastereomers. The present invention contemplates all possible optical isomeric forms of structural formula I given above. Individual enantiomeric or diastereomeric forms of the compounds of this invention may be obtained from mixtures by known methods of resolution.

In a preferred embodiment, compounds of formula I are those wherein Y is hydrogen.

In another preferred embodiment, compounds of formula I are those wherein n is zero and X is —CHR₅, where R₅ is as defined above.

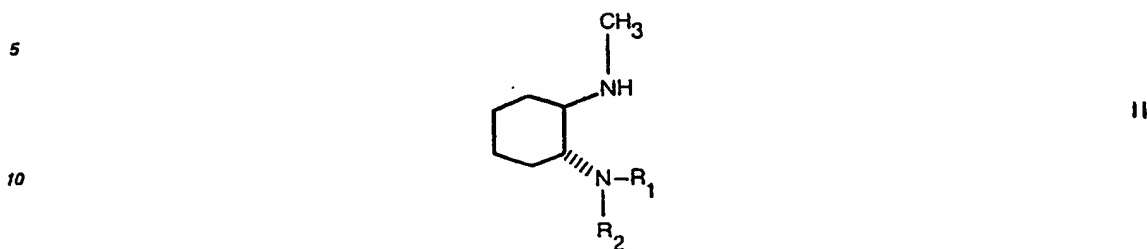
In yet another preferred embodiment, compounds of formula I are those wherein Y is sulfur or =NR₇, where R₇ is as defined above.

Examples of compounds contemplated as falling within the scope of the present invention are the following:

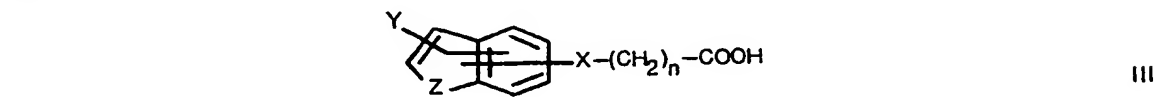
trans-N,2-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofuranacetamide;
trans-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-N-methyl-N-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(methyl(2-propenyl)amino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-N-methylbenzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(methyl(2-propynyl)amino)cyclohexyl]-benzo[b]thiophene-4-acetamide;
trans-N-methyl-7-propyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thienyl)benzo[b]thiophene-7-acetamide;
trans-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-5-acetamide;
trans-N-methyl-N-[2-(1-piperidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(methyl[(tetrahydro-2-furanyl)methyl]amino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(methyl(3-methyl-2-butenyl)amino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-[2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl]-methylbenzo[b]thiophene-4-acetamide;
trans-N,5-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-5-chloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[b]thiophene-2-propionamide;
trans-2-(benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-2-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-propanamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-butanamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-1-acetamide;
trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N,2,3-trimethyl-1*H*-indole-5-acetamide;
trans-2,3,4,9-tetrahydro-N,9-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-carbazole-6-acetamide;

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In general, compounds of the present invention are prepared by reacting the appropriate *trans*-1,2-diaminocyclohexane of the structural formula II

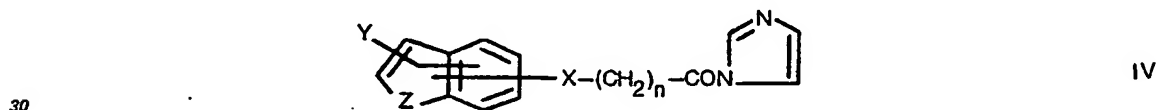


15 with a carboxylic acid of structural formula III



or a reactive derivative formed from such a carboxylic acid.

The appropriate carboxylic (III) may be reacted directly with the amine with the aid of such reagents as dicyclohexylcarbodiimide and the like. Alternatively, the carboxylic acids are first converted to a reactive derivative such as an activated ester, anhydride, acid halide such as the bromide or chloride, or acyl imidazoles of the formula IV



and the resulting carboxylic acid derivative reacted with the substituted *trans*-1,2-diaminocyclohexane (II).

For example, the reaction between the cyclic diamine (II) and the appropriate carboxylic acid (III) is carried out in the presence of the coupling reagent, dicyclohexylcarbodiimide, in a cyclic ether solvent such as tetrahydrofuran or dioxane until the desired product is formed. The reaction will generally proceed at ambient temperatures but, depending upon the reactivity of the specific materials involved, the desired reaction time, the solvent being employed, and the molar proportions of reagents, the reaction temperature may be varied between about -25°C and the reflux temperature of the solvent employed.

The reaction between the acid halide and the cyclic diamine (II) is carried out, generally at ambient temperature, in a suitable solvent in the presence of an acid acceptor such as tertiary amine or an alkali metal or alkaline earth metal carbonate or bicarbonate. The mixture of the amine and the acid halide is allowed to stand until reaction is complete.

When the reaction between the cyclic diamine (II) and the acid (III) or acid derivative has proceeded to substantial completion, the desired product is recovered from the reaction mixture by techniques well known to practitioners of the organic chemical arts.

For example, the reaction mixture can be evaporated under vacuum, if desired, to remove the solvent and other volatile components of the reaction mixture to yield the product, generally as an oil. This residual material is then taken up in a solvent such as diethyl ether, washed first with a salt solution such as sodium bicarbonate solution and then with water. Separation of the organic phase, drying over, for example anhydrous magnesium sulfate, and evaporation of the ether solvent, yields the desired product, usually as an oil or crystalline solid.

The starting *trans*-1,2-diaminocyclohexane compounds of the present invention are prepared by the method detailed in United States Patent 4,145,435. The carboxylic acids (III) are known, or if novel, are prepared by reaction sequences well known in the art. The acyl imidazole derivatives (IV) of the carboxylic acids are prepared by reacting carbonyldiimidazole with the appropriate acid.

The free base form of the compounds of this invention are readily converted, if desired, by known methods to the acid addition salts by reaction with any of a number of inorganic or organic acids including hydrochloric, hydrobromic, hydriodic, sulfuric, nitric, phosphoric, acetic, benzoic, citric, maleic tartaric, succinic, gluconic, ascorbic, sulphamic, oxalic, pamoic, methanesulfonic, benzenesulfonic, and related acids and mixtures thereof. The free base form of the compounds of the present invention and the acid addition salt may differ in certain of their physical properties, such as solubility in polar solvent, but are otherwise equivalent for the purposes of this invention.

The compounds of the present invention possess significant analgesic activity with potential for minimum dependence liability due to their selective kappa opioid receptor binding properties. In addition to analgesics, selective kappa agonists also cause opioid receptor-mediated sedation, diuresis, and

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corticosteroid elevations. Accordingly, the compounds of the present invention may also be useful diuretics and psychotherapeutic agents as well as analgesics.

Representative examples of the compounds of formula I have shown positive activity in standard laboratory analgesic tests such as writhing and hot plate with animals such as mice. For example, compounds of Examples 1 and 2 when given at 10 mg/kg s.c. (subcutaneous administration) of animal body weight, caused abolition of writhing in the acetylcholine-induced writhing test. When compared with control, mice also showed longer tolerance of heat on a hot plate at 55°C when given 10 mg/kg s.c. of the compound of Example 1.

Representative examples of the compounds of the present invention, when tested *in vitro* to determine the extent of opioid receptor binding, were found to be selectively bound to the kappa receptors with evidence of little or no binding to the mu and delta receptors. The benefits of this selective binding has already been mentioned above and is also described by M. B. Tyers, *Br. J. Pharmac.* (1980) 69:503—512.

Measurement of the kappa opioid receptor site binding activity of compounds of the present invention was made by the following method. Guinea pig brain homogenates were prepared fresh each day utilizing the method of Gillan, et al, *Br. J. Pharm.*, 70:481—490 (1980).

The binding of tritiated etorphine to brain homogenates was measured in the presence of unlabelled competitor compounds of the present invention with 200 nanomolar D-Ala-D-Leu-enkephalin (acronym DADLE) and 200 nanomolar D-Ala-MePheGly-ol-enkephalin (acronym DAGO) added to saturate the delta and mu opioid receptors, respectively. The reaction was terminated by rapid filtration and the radioactivity bound to the filters counted by liquid scintillation spectrophotometry.

Measurement of the mu and delta opioid receptor site binding activity of compounds of the present invention was made by the following method. Guinea pig homogenates were prepared fresh each day utilized the method of Gillan, et al., cited above.

Homogenates were incubated for 150 minutes at 0°C with either tritiated DAGO to measure mu receptor site binding activity, or with tritiated DADLE in the presence of a ten-fold excess of unlabelled DAGO to measure delta opioid receptor site activity. Nonspecific binding was determined in the presence of 10^{-6} M DAGO and 10^{-6} M DADLE.

Reactions were terminated by rapid filtration and the radioactivity bound to the filters counted by liquid scintillation spectrophotometry.

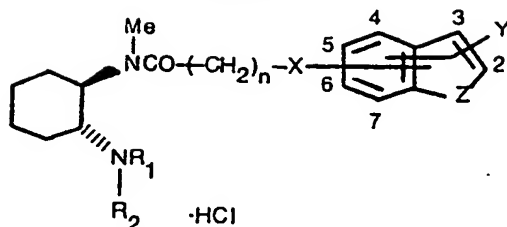
Data was analyzed by the methods of Scatchard, *Ann. N.Y. Acad. Sci.*, 51:660—672 (1949) and Hill, *J. Physiol.*, 40:IV—VIII (1910). The inhibition of binding of tritiated etorphine, DAGO and DADLE by cold ligands was determined from the regression of log percentage inhibition of specific binding or log concentration of cold ligand. The inhibition constant (K_i) was calculated from the equation:

$$K_i = \frac{IC_{50}}{1 + [L]/KD}$$

where [L] is the concentration of the labelled ligand and K_D , its equilibrium dissociation constant.

The results of these tests for several representative compounds of the present invention are presented in Table I.

TABLE I



R1 R2	n	x	z	y	(Ki M) Kappa	Mu
c-C ₄ H ₈	0	4-CH ₂	S	H	3.73x10 ⁻⁹	4.08x10 ⁻⁷
c-C ₄ H ₈	0	5-CH ₂	NCH ₃	2,3-c-C ₄ H ₈	3.97x10 ⁻⁶	4.67x10 ⁻⁷
c-C ₄ H ₈	0	3-CH ₂	NH	H	7.45x10 ⁻⁸	2.94x10 ⁻⁶
c-C ₄ H ₈	0	3-CH ₂	S	H	4.85x10 ⁻⁸	>10 ⁻⁶
CH ₃ , H	0	4-CH ₂	S	H	10 ⁻⁶ -10 ⁻⁷	>10 ⁻⁶
c-C ₄ H ₈	1	3-CH ₂	NH	H	>>10 ⁻⁶	>>10 ⁻⁶
CH ₃ , CH ₂ -	0	4-CH ₂	S	H	~10 ⁻⁷	10 ⁻⁶ -10 ⁻⁷
c-C ₃ H ₅						
CH ₃ , CH ₂ CH:	0	4-CH ₂	S	H	~10 ⁻⁷	2.1x10 ⁻⁷
CH ₂ .						
c-C ₄ H ₈	2	3-CH ₂	NH	H	>10 ⁻⁶	NT
c-C ₄ H ₈	0	3-CH ₂	O	2-CH ₃	7.89x10 ⁻⁸	~10 ⁻⁵
c-C ₄ H ₈	0	3-CH ₂	CH ₂	H	~10 ⁻⁷	~10 ⁻⁵
c-C ₄ H ₈	0	5-CH ₂	O	3-Ph	~10 ⁻⁶	~10 ⁻⁵
c-C ₄ H ₈	0	2-CH ₂	CH ₂	H	~10 ⁻⁵	~10 ⁻⁵ -10 ⁻⁶
c-C ₄ H ₈	0	7-CH ₂	S	3-(2'-	~10 ⁻⁵	NT
				thiophene)		
c-C ₄ H ₈	0	5-CH ₂	S	3-Ph	~10 ⁻⁵	NT
c-C ₄ H ₈	0	4-CH ₂	S	7-nPr	4.24x10 ⁻⁸	1.82x10 ⁻⁷
c-C ₅ H ₁₀	0	4-CH ₂	S	H	2.45x10 ⁻⁷	2.41x10 ⁻⁶
CH ₃ , 2-tetra-	0	4-CH ₂	S	H	10 ⁻⁶ -10 ⁻⁷	NT
hydrofur-						
furyl						
c-C ₄ H ₈	0	4-CHMe	S	H	>10 ⁻⁶	NT
CH ₃ , CH ₂ CH:	0	4-CH ₂	S	H	2.05x10 ⁻⁷	3.25x10 ⁻⁸
CMe ₂						

The abbreviation "c-C₄H₈" represents the divalent butylene radical. When R₁ and R₂ represent the butylene radical, then together with the nitrogen atom to which they are attached, they form a pyrrolidiny ring. The group "c-C₅H₁₀" represents the divalent pentamethylene radical. When R₁ and R₂ represent the pentamethylene radical, then together with the nitrogen atom to which they are attached, they form a piperidyl ring.

The compounds of the present invention, and/or the nontoxic, pharmaceutically acceptable salts thereof, may be administered to mammals in pharmaceutical compositions or formulations which

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comprise one or more of the compounds of this invention and/or the nontoxic, pharmaceutically acceptable, nontoxic carrier.

The compounds of this invention may be administered parenterally in combination with conventional injectable liquid carriers such as sterile pyrogen-free water, sterile peroxide-free ethyl oleate, dehydrated
5 alcohols, propylene glycol, and mixtures thereof.

Suitable pharmaceutical adjuvants for the injecting solutions include stabilizing agents, solubilizing agents, buffers, and viscosity regulators. Examples of these adjuvants include ethanol, ethylenediamine tetraacetic acid (EDTA), tartrate buffers, citrate buffers, and high molecular weight polyethylene oxide viscosity regulators. These pharmaceutical formulations may be injected intramuscularly,
10 intraperitoneally, or intravenously.

Compounds of the present invention, and/or the nontoxic, pharmaceutically acceptable salts thereof, may be administered to mammals orally in combination with conventionally compatible carriers in solid or in liquid form. These oral pharmaceutical compositions may contain conventional ingredients such as binding agents selected from the group consisting of syrups, acacia, gelatin, sorbitol, tragacanth, polyvinyl-
15 pyrrolidone, and mixtures thereof. The compositions may further include fillers such as lactose, mannitols, starch, calcium phosphate, sorbitol, methylcellulose, and mixtures thereof.

These oral compositions may also contain lubricants such as magnesium stearate, high molecular weight polymers such as polyethylene glycol, high molecular weight fatty acids such as stearic acid silica, or agents to facilitate disintegration of the solid formulation, such as starch, and wetting agents such as
20 sodium lauryl sulfate.

The oral pharmaceutical compositions may take any convenient form such as tablets, capsule, lozenges, aqueous or oily suspensions, emulsions, or even dry powders which may be reconstituted with water and/or other liquid media prior to use.

Compounds of the present invention and/or the nontoxic, pharmaceutically acceptable salts thereof
25 may be administered topically in the form of an ointment or cream containing from about 0.1% to 10% by weight of the active component in a pharmaceutical ointment or cream base.

Compounds of the present invention and/or the nontoxic, pharmaceutically acceptable salts thereof, may be administered to mammals rectally in the form of suppositories. For preparing suppositories, a low-melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active
30 ingredient is dispersed homogeneously therein by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

The solid or liquid forms may contain flavorants, sweeteners, and/or preservatives such as alkyl p-hydroxybenzoates. The liquid forms may further contain suspending agents such as sorbitol, glucose, or other sugar syrups, methyl-, hydroxymethyl-, or carboxymethylcellulose, and gelatin, emulsifying agents
35 such as lecithin or sorbitol monooleate, and conventional thickening agents. The liquid compositions may optionally be encapsulated in, for example, gelatin capsules, in an effective amount.

Preferably, the pharmaceutical compositions of this invention are in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate amounts of the active component. The unit doses form can be packaged preparation with the package containing discrete quantities of the
40 preparation. For example, the package may take the form of packeted tablets, capsules, and powders in envelopes, vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself or can be the appropriate number of any of these packaged forms.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 0.5 mg to about 350 mg according to the particular application and the potency of the active ingredient.

When employed systematically in therapeutic use as analgesic agents in the pharmaceutical method of this invention, the compounds are administered at doses of about 0.05 mg to 2.0 mg of active compound
45 per kilogram of body weight of the recipient.

General synthetic methods for preparing compounds of the present invention wherein R₁ and R₂, taken together, form a pyrrolidiny ring are given below in Methods A—D. Examples 1—30 illustrate the
50 preparation of particular compounds in accordance with the present invention.

General Synthetic Methods

Preparation of amide monohydrochlorides (2 mmol scale)

Method A: *Trans-N*-methyl-2-(1-pyrrolidinyl) cyclohexanamine (364 mg, 2 mmol) in methylene
55 chloride (5 ml) was added with stirring to a solution of the acid chloride [prepared by the action of thionyl chloride (5 ml) on the appropriate carboxylic acid (2 mmol)] in methylene chloride (20 ml). After stirring for ten minutes, the mixture was evaporated to small volume and diethyl ether added until no more precipitate appeared. The product was collected by filtration, washed with diethyl ether, and dried in a vacuum oven at 70°C overnight.

Method B: *Trans-N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine (364 mg, 2 mmol) in methylene chloride
60 (5 ml) was added with stirring to a solution of the acid chloride [prepared by the action of thionyl chloride (5 ml) on the appropriate carboxylic acid (2 mmol)] in a 1:1 mixture of methylene chloride and diethyl ether (20 ml). After stirring for ten minutes, diethyl ether was added until no more precipitate appeared. The product was collected by filtration, washed with diethyl ether, and dried in a vacuum oven at 70°C
65 overnight.

Method C: A solution of carbonyl di-imidazole (356 mg, 2.2 mmol) in dry tetrahydrofuran (10 ml) was added to a solution of the appropriate carboxylic acid (2 mmol) in tetrahydrofuran (20 ml). The mixture was stirred for 30 minutes at room temperature. *Trans-N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine (364 mg, 2 mmol) in tetrahydrofuran (10 ml) was added, the mixture heated to reflux, then stirred at room temperature for 16 hours. The reaction was evaporated to small volume, and the residue dissolved in ethyl acetate (100 ml). The extract was washed with saturated sodium bicarbonate (3 × 50 ml), then water (50 ml), dried (MgSO₄), and evaporated under reduced pressure.

Method D: Substantially as described in Method C with the exception that the mixture of reactants was stirred at ambient temperature for 16 hours rather than being heated under reflux.

The following examples are provided to enable one skilled in the art to practice the present invention. The examples are not to be read as limiting the scope of the invention as defined by the appended claims, but as merely illustrative thereof.

Example 1

Preparation of *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide

A. Preparation of 7-methyl-7-azabicyclo[4.1.0]heptane [Modification of method of T. Taguchi and M. Eto., *J. Amer. Chem. Soc.* 80, 4076 (1958)].

i. Cyclohexene oxide (Aldrich, 196.3 g 2M) was added to a 25/30% solution of aqueous methylamine (745 ml, 6M) (25% solution) dropwise with stirring and cooling in an icebath over one hour, during which time the temperature reached 46°C. The solution was stirred at room temperature overnight, and then refluxed for three hours in fume hood. The solution was cooled in an icebath and saturated with solid NaOH, extracted with 4 × 200 ml ether, dried (MgSO₄) and evaporated to dryness on rotary evaporator.

The crude product, *trans*-2-(methylamino)cyclohexanol, was distilled under water vacuum pressure, the first small sample of cyclohexene epoxide discarded. The bulk was distilled from a 1-liter flask with a 60W isomantle and a short Leibig condenser over a two hour period to yield the product.

bp 118°C (water vacuum)
yield: 208 g (81%)

ii. *Trans*-2-(methylamino)cyclohexanol (208 g 1.61 M) was placed in a three liter beaker and dissolved in ether (400 ml). Chlorosulphonic acid (1.89 g, 1.62 M) was added dropwise to the ice-salt cooled solution. Added a further 200 ml of ether. The solution was hand stirred. Addition took one hour. The solution/solid was allowed to warm to room temperature and stand for three hours. The ether was decanted and the white salt washed with 300 ml ether which was also decanted.

The solid was cooled in ice-salt bath and NaOH (218 g in one liter water) added slowly. The thick white solid was left at room temperature overnight.

The crude product, 7-methyl-7-azabicyclo [4.1.0] heptane, was distilled in isomantle with continuous addition of water from separating funnel to retain approximately original volume. After 600 ml of liquid had been collected, the total distillate was saturated with solid NaOH, extracted with 5 × 200 ml ether, dried (MgSO₄) and evaporated on rotary evaporator.

The product was distilled using a water vacuum and air bleed, the collection vessel being cooled in an ice bath.

Yield: 67 g (37%), b.p. 38°C (water vacuum and bleed)

iii. Preparation of *trans-N*-Methyl-2-(1-pyrrolidinyl)cyclohexanamine

A mixture of 7-Methyl-7-azabicyclo[4.1.0]heptane (7.0 g, 0.063 M), pyrrolidine (17.92 g, 0.25 M), water (10 ml) and ammonium chloride (0.16 g) was stirred and refluxed for 21 hours. The solution was cooled and solid sodium hydroxide added and extracted with ether (3 × 50 ml). The extracts were dried over magnesium sulphate and evaporated under reduced pressure to a brown oil. This was distilled under high vacuum to yield a colorless oil.

bp: 95°C (6.0 g)

B. Preparation of *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

By Method B, benzo[b]thiophene-4-acetic acid (192 mg, 1 mmol) was converted to the *amide monohydrochloride* (376 mg, 96%); $V_{\max}C = 1640 \text{ cm}^{-1}$.

Example 2

Preparation of *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)-*p*-cyclohexyl]-1*H*-indole-3-acetamide monohydrochloride

A. *Trans-N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine was prepared as described in example 1 above.

B. Preparation of *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indol-3-acetamide monohydrochloride.

Trans-N-methyl-2-(1-pyrrolidinyl)cyclohexanamine (0.368 g) was dissolved in methylene chloride (10 ml) and stirred at room temperature. The acid chloride of 3-indole acetic acid (prepared by the action of thionyl chloride on 3-indole acetic acid, 0.35 g) dissolved in methylene chloride (10 ml) was added and let stand for five hours. Ether was added to rapidly stirred solution until no more precipitate appeared. After

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further rapid stirring for one hour, the precipitate was filtered and dried in a vacuum oven at 90°C for one hour and stored in a predried bottle. The product was in the form of a black glassy solid (300 mg).

Example 3

- 5 Preparation of *trans*-*N*-methyl-*N*-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-acetamide free base
1*H*-Indole 3-acetic acid (1.05 g, Aldrich) and *trans*-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine were dissolved in tetrahydrofuran (30 ml) and cyclohexyl carbodiimide (1.24 g) added. The resultant solution was stirred at room temperature overnight, during which time a white precipitate appeared.
The solution was filtered and evaporated to an oil, which was chromatographed on silica. Elution with
10 ether gave the product as a white solid (1.3 g), mp 175—178°C.

Example 4

- Trans*-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-propanamide monohydrochloride
By Method C, indole-3-propanoic acid (0.752 g, 4 mmol) was converted to the *amide*
15 *monohydrochloride* (0.65 g, 42%) isolated as white crystals, mp 143.5—145°C.

Example 5

- Trans*-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-butanamide dihydrogen sulphate
By Method D, indole-3-butyric acid (406 mg, 2 mmol) was treated with carbonyl diimidazole (356 mg, 2
20 mmol) and the diamine (364 mg, 2 mmol). After standing for 16 hours at room temperature the mixture was refluxed for a further 20 hours. The crude product was purified by column chromatography [silica gel eluted with CH₂Cl₂:EtOH:0.880 NH₃, 18:2:1, lower layer] to give the pure free base. The dihydrogen sulphate salt was then prepared by the addition of an ethereal solution of the amine, giving the product as a very hygroscopic solid (190 mg, 20%); Vmax 1635 cm⁻¹.

Example 6

- Trans*-(+)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-1-acetamide
Triethylamine (139 µl, 1 mmol) was added to a solution of 1*H*-indole-1-acetic acid (175mg, 1 mmol) in tetrahydrofuran (10 ml) at -15°C with vigorous stirring. Ethyl chloroformate (96 µl, 1 mmol) was added, and the mixture stirred for five minutes. A solution of *trans*-(±)-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine
30 (182 mg, 1 mmol) in tetrahydrofuran (2 ml) was added, and stirring continued for 30 minutes at -15°C, then 30 minutes at room temperature. The reaction was evaporated to small volume, the residue dissolved in ethyl acetate (50 ml), and washed with saturated sodium bicarbonate solution (3 × 50 ml). The organic extract was dried (MgSO₄), evaporated under reduced pressure, and recrystallized from diethyl ether/methylene chloride to yield the *amide* (100 mg, 32%); Vmax C = 0 1635 cm⁻¹.

Example 7

- Trans*-(±)-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-*N*,2,3-trimethyl-1*H*-indole-5-acetamide
Triethylamine (139 µl, 1 mmol) was added to a solution of 2,3-dimethyl-1*H*-indole-5-acetic acid (203 mg, 1 mmol) in tetrahydrofuran (10 ml) at -15°C, with vigorous stirring. Ethyl chloroformate (96 µl, 1 mmol)
40 was added, and the mixture stirred for five minutes. A solution of *trans*-(±)-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine (182 mg, 1 mmol) in tetrahydrofuran (2 ml) was added, and stirring continued for 30 minutes at -15°C, then 30 minutes at room temperature. The reaction was evaporated to small volume, the residue taken into ethyl acetate (50 ml), and washed with saturated sodium bicarbonate solution (3 × 50 ml). The organic extract was dried (MgSO₄), evaporated under reduced pressure and
45 recrystallized from ethyl acetate to yield the *amide* (204 mg, 56%); VmaxC = 0 1615 cm⁻¹.

Example 8

- Trans*-(±)-*N,N'*-dimethylcyclohexane-1,2-diamine
A vigorously stirred mixture of *N*-methylazabicyclo-[4.1.0]-heptane (36.1 g), monomethylamine (162 ml of a 23—30% aqueous solution) and ammonium chloride (0.50 g) was heated in an oil bath at 94—99°C for
50 21.5 hours. After cooling to 0°C the mixture was treated with sodium hydroxide (10 g) and extracted with diethylether (4 × 100 ml). The combined ethereal fractions furnished a residue which was distilled to give pure *trans*-(±)-*N,N'*-dimethyl-cyclohexane-1,2-diamine (18 g, 39%); b.p. 78°C (14 mm) which solidified after standing at 17°C; found: C, 67.5; H, 13.1; N, 19.65. Calc. for C₈H₁₈N₂: C, 67.55, H, 12.75; N, 19.7.

Example 9

- Trans*-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride
A solution of benzo[b]thiophene-4-acetic acid (4.65 g, 24 mmol) and carbonyldiimidazole (3.95 g, 24 mmol) in tetrahydrofuran (20 ml) was heated to reflux for 0.5 hours, then cooled to 0°C and added dropwise over 25 minutes to a stirred solution of *trans*-(±)-*N,N'*-dimethylcyclohexane-1,2-diamine (3.0 g, 21 mmol) in
60 tetrahydrofuran (10 ml) at -13°C. The mixture was stirred for a further two hours and allowed to warm to room temperature. The solvent was removed in vacuo to give residue which was dissolved in dichloromethane (100 ml) and washed with aqueous potassium carbonate (100 ml) then water (100 ml). The organic fraction furnished an oily residue which after high pressure liquid chromatography (Waters 500 Prep HPLC silica gel, 80:20:1 ethyl acetate-methanol-triethylamine) gave a light yellow oil (3.3 g); Vmax (liquid file) 3320, 1635 cm⁻¹.

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Formation of hydrochloride salt: *Method L*: The oil (3.3 g) was dissolved in diethyl ether (100 ml), filtered through a plug of cotton wool and treated with a solution of hydrogen chloride in diethyl ether until the solution became acidic. The resulting white precipitate was isolated by filtration and washed with diethyl ether. This procedure furnished *trans*-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride (3.0 g, 40%).

Example 10

Trans-(±)-*N*-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-*N*-methylbenzo[b]thiophene-4-acetamide monohydrochloride

A solution of *trans*-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride (200 mg, 0.57 mmol) in dichloromethane (10 ml) was treated with 10% aqueous potassium carbonate to liberate the parent amine. This oil was dissolved in dichloromethane (1 ml) and triethylamine (0.15 ml, 1.1 mmol) treated with bromomethylcyclopropane (220 mg, 1.6 mmol) and heated to reflux for 26 hours. After standing at room temperature for 70 hours the mixture was poured into 10% aqueous potassium carbonate (10 ml) and extracted with dichloromethane (3 × 15 ml) to give an oil which after silica gel chromatography (100:1 ethyl acetate:triethylamine) furnished *trans*-(±)-*N*-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-*N*-methylbenzo[b]thiophene-4-acetamide (200 mg, 95%) δ_H (CDCl₃) 0.7—0.0 (5H, m); V_{max} (liquid film) 3080, 1635 cm⁻¹.

The hydrochloride salt of this oil (250 mg) was prepared as described in Method L and recrystallized (dichloromethane-diethyl ether) to give a white solid (200 mg, 73%); m.p. 229—234°C.

Example 11

Trans-(±)-*N*-methyl-*N*-[2-[methyl(2-propenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

A solution of *trans*-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride (400 mg, 1.13 mmol) in dichloromethane (10 ml) was treated with aqueous potassium carbonate (30 ml) to liberate the parent amine. This oil was dissolved in ethanol (10 ml), dichloromethane (1 ml) and triethylamine (0.3 ml, 2.2 mmol) and treated with allyl bromide (257 mg, 2.1 mmol). This mixture was stirred in an oil bath at 50—60°C for six hours, concentrated in vacuo and partitioned between 10% aqueous potassium carbonate and dichloromethane. The organic fractions furnished an oil which after silica gel chromatography (100:1 ethyl acetate:triethylamine) gave *trans*-(±)-*N*-methyl-*N*-[2-[methyl(2-propenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide (270 mg, 67%); δ_H (CDCl₃) 6.0—4.3 (3H, m); V_{max} (liquid film) 1637 cm⁻¹.

The hydrochloride salt was prepared as described in Method L and recrystallized (dichloromethane-diethyl ether) to give a white solid (170 mg; 57%); m.p. 209—211.5°C.

Example 12

Trans-(±)-*N*-methyl-2-(1-piperidinyl)cyclohexanamine

A stirred mixture of *N*-methylazabicyclo[4.1.0]heptane (5.0 ml, 39 mmol), piperidine (3.9 ml, 39 mmol) and ammonium chloride (0.2 g dissolved in 0.4 ml water) was heated to reflux for 5.5 h. Bulb to bulb distillation yielded *trans*-(±)-*N*-methyl-2-(1-piperidinyl)cyclohexanamine as a colourless liquid (oven temperature 210°/20 mm) (3.2 g, 42%); δ_H (CDCl₃) 2.34 (3H, s).

Example 13

Trans-(±)-*N*-methyl-*N*-[2-(1-piperidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

A stirred solution of benzo[b]thiophene-4-acetic acid (0.50 g, 2.6 mmol) and carbonyl di-imidazole (0.46 g, 2.8 mmol) in tetrahydrofuran (5 ml) was heated with a solution of *trans*-(±)-*N*-methyl-2-(1-piperidinyl)cyclohexanamine (0.46 g, 2.3 mmol) in tetrahydrofuran (2 ml). This mixture was heated to reflux for five minutes, concentrated in vacuo, poured into saturated aqueous sodium bicarbonate (30 ml) and extracted with dichloromethane (2 × 20 ml) to give an oil which on trituration with diethyl ether gave *trans*-(±)-*N*-methyl-*N*-[2-(1-piperidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide as a crystalline solid (610 mg, 72%); V_{max} = 0 (liquid film) 1635 cm⁻¹.

The hydrochloride salt of this amine (370 mg, 1.0 mmol) was prepared as described in Method L and recrystallized (dichloromethane-diethyl ether) to give a white solid (0.40 g, 98%).

Example 14

Trans-(±)-*N*-methyl-*N*-[2-[methyl[(tetrahydro-2-furanyl)methyl]amino]cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

A solution of *trans*-(±)-*N*-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride (120 mg, 0.34 mmol) in dichloromethane (10 ml) was treated with saturated aqueous sodium bicarbonate to liberate the parent amine. The oil was dissolved in dimethyl formamide and treated with tetrahydrofurfuryl bromide (68 mg, 0.41 mmol) and sodium bicarbonate (43 mg, 0.5 mmol). The resulting mixture was stirred in an oil bath at 95—110°C for 20 hours then concentrated in vacuo, poured into saturated aqueous sodium bicarbonate (15 ml) and extracted with dichloromethane (2 × 15 ml). Silica gel chromatography (70:30:1 ethyl acetate:hexane-triethylamine) furnished *trans*-(±)-

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N - methyl - *N* - (2 - (methyl((tetrahydro - 2 - furanyl)methyl)amino)cyclohexyl)benzo[b]thiophene - 4 - acetamide as a colourless oil (43 mg, 32%); *m/e*: 400 (M+), 329, 286, 195, 147; t.l.c. analysis of this product (50:50:1 ethyl acetate-hexane-triethylamine, multiple development) indicated that it consisted of two components.

- 5 The hydrochloride salt of this amine (42 mg, 0.10 mmol) was prepared as described in Method L to give a white solid (13 mg, 28%).

Example 15

2-(4-benzo[b]thiophene)propionic acid

- n*-Butyl lithium (4.0 ml of a 1.6 *M* solution in hexane, 6.4 mmol) was added to a stirred solution of benzo[b]thiophene-4-acetic acid (0.60 g, 3.1 mmol) in tetrahydrofuran (10 ml) and dimethyl sulphoxide (4 ml) with cooling in ice water. After 40 minutes at 0°C the resulting solution was treated with methyl iodide (190 µl, 3.1 mmol) and stirred at room temperature for 3.3 hours. Concentration in vacuo furnished a red oil which was poured into 5% aqueous sodium hydroxide (50 ml) and washed with diethyl ether (3 × 30 ml). The aqueous fraction was acidified with concentrated nitric acid and extracted with dichloromethane (3 × 50 ml) to give a red oil (0.65 g) which after silica gel chromatography (70:30 ethyl acetate-hexane + 0.5% acetic acid) gave 2-(4-benzo[b]thiophene)propionic acid as an off-white solid (0.26 g, 38%); δ_H (CDCl₃) 11.4 (1H, s); 8.0—7.0 (5H, m); 4.28 (1H, q, *J* 7 Hz); 1.62 (3H, d, *J* 7 Hz).

Example 16

- 20 Trans-(±)-*N*-methyl-*N*-(2-pyrrolidiny)cyclohexyl)-4-benzo[b]thiophene-2-propionamide

- A stirred solution of 2-(4-benzo[b]thiophene)propionic acid (98 mg, 0.47 mmol) and carbonyl diimidazole (78 mg, 0.48 mmol) in tetrahydrofuran (0.5 ml) was heated to reflux 0.5 hours then cooled to room temperature and treated with a solution of *trans*-(±)-*N*-methyl-2-(1-pyrrolidinyl)cyclohexanamine (76 mg, 0.42 mol) in tetrahydrofuran (0.5 ml). This mixture was heated to reflux for 5.5 hour, poured into saturated aqueous sodium bicarbonate (30 ml) and extracted with dichloromethane (2 × 20 ml) to give an oil which after silica gel chromatography (50:50:1 ethyl acetate-hexane-triethylamine) furnished *trans* - (±) - *N* - methyl - *N*-(2 - pyrrolidinyl - cyclohexyl) - 4 - benzo[b]thiophene - 2 - propionamide (100 mg, 64%); $V_{max}C = 0$ (liquid film) 1638 cm⁻¹; t.l.c. analysis of this produce (50:50:1 ethyl acetate-hexane-triethylamine) indicated that it consisted of two components. The hydrochloride salt of this diastereoisomeric mixture of amines (80 mg, 0.22 mmol) was prepared as described in Method L to give a white solid (70 mg, 78%).

Example 17

Trans-(±)-*N*-(2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl)-*N*-methyl-benzo[b]-thiophene-4-acetamide monohydrochloride and *trans*-(±)-*N*-(2-methyl(3-methyl-2-butenyl)amino)cyclohexyl)benzo[b]thiophene-4-acetamide monohydrochloride

- A stirred solution of *trans* (±) - *N* - methyl - *N* - [2 - (methylamino)cyclohexyl]benzo[b]thiophene - 4 - acetamide (330 mg, 1.04 mmol) in dichloromethane (2 ml) was treated with 1-bromo-3-methyl-but-2-ene (140 µl) and sodium bicarbonate (160 mg, 1.9mmol) and heated to reflux for 1.5 hours. The mixture was poured into saturated aqueous sodium bicarbonate (10 ml) and extracted with dichloromethane (2 × 10 ml). Silica gel chromatography (70:30:1 ethyl acetate-hexane-triethylamine) furnished an oil (260 mg, 65%); $V_{max}C = 0$ (liquid film) 1640 cm⁻¹, which was homogeneous by t.l.c. analysis (70:30:1 ethyl acetate-hexane triethylamine) but analysis by ¹H n.m.r. indicated the presence of the parent amines of the above two compounds.

- The hydrochloride salts were formed as described in Method L and recrystallized (dichloromethane-diethyl ether) to give a white solid (0.27 g, 94%); ¹H-n.m.r. (CDCl₃) integration indicates the presence of *trans* - (±) - *N* - (2 - [(1,1 - dimethyl - 2 - propenyl)methylamino] - cyclohexyl - *N* - methyl - benzo[b]thiophene - 4 - acetamide monohydrochloride and *trans* - (±) - *N* - methyl - *N* - (2 - [methyl(3 - methyl - 2 - butenyl)amino]cyclohexyl)benzo[b]thiophene - 4 - acetamide monohydrochloride in a 5:2 ratio respectively.

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Example 18

Trans-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide monohydrochloride

- By Method A, benzo[b]thiophene-3-acetic acid (384 mg, 2 mmol) was converted to the amide monohydrochloride (716 mg, 91%); $V_{max}C = 0$ 1645 cm⁻¹.

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Example 19

Trans-(±)-*N*,2-dimethyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofurancetamide monohydrochloride

- By Method A, 2-methyl-3-benzofuranacetic acid (380 mg, 2 mmol) was converted to the amide monohydrochloride (606 mg, 78%); $V_{max}C = 0$ 1645 cm⁻¹.

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Example 20

Trans-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-3-acetamide monohydrochloride

- By Method C, 1*H*-indene-3-acetic acid (174 mg, 1 mmol) was converted to the amide. The crude product was dissolved in methylene chloride (5 ml) and treated with a solution of hydrogen chloride in diethyl ether until the solution became acidic. Diethyl ether was then added until no more precipitate appeared. The

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product was collected by filtration, washed with diethyl ether and dried in a vacuum at 70°C overnight, to yield the amide monohydrochloride (80 mg, 21%); $V_{\max}C = 0\ 1640\ \text{cm}^{-1}$.

Example 21

Trans-(±)-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofurancetamide monohydrochloride

By Method B, 3-phenyl-5-benzofuranacetic acid (252 mg, 1 mmol) was converted to the amide monohydrochloride (363 mg, 80%); $V_{\max}C = 0\ 1640\ \text{cm}^{-1}$.

Example 22

Trans-(±)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indene-2-acetamide monohydrochloride

By Method C, 1H-indene-2-acetic acid (174 mg, 1 mmol) was converted to the amide. The crude product was dissolved in methylene chloride (3 ml) and treated with a solution of hydrogen chloride in diethyl ether until the solution became acidic. Diethyl ether was then added until no more precipitate appeared. The product was collected by filtration, washed with diethyl ether and dried in a vacuum oven at 70°C overnight, to yield the amide monohydrochloride (110 mg, 29%); $V_{\max}C = 0\ 1645\ \text{cm}^{-1}$.

Example 23

Trans-(±)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thienyl)benzo[b]thiophene-7-acetamide monohydrochloride

By Method C, 3-(2-thienyl)benzo[b]thiophene-7-acetic acid (215 mg, 0.78 mmol) was converted to the amide. The crude product was dissolved in methylene chloride (3 ml) and treated with a solution of hydrogen chloride in diethyl ether until the solution became acidic. Diethyl ether was then added until no further precipitate appeared. The product was collected by filtration, washed with diethyl ether, and dried in a vacuum oven at 80°C overnight, to yield the amide monohydrochloride (200 mg, 54%); $V_{\max}C = 0\ 1635\ \text{cm}^{-1}$.

Example 24

Trans-(±)-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-5-acetamide monohydrochloride

By Method B, 3-phenylbenzo[b]thiophene-5-acetic acid (268 mg, 1 mol) was converted to the amide monohydrochloride (329 mg, 70%); $V_{\max}C = 0\ 1645\ \text{cm}^{-1}$.

Example 25

Trans-(±)-N-methyl-7-propyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride

By Method B, 7-propylbenzo[b]thiophene-4-acetic acid (234 mg, 1 mmol) was converted to the amide monohydrochloride (423 mg, 97%); $V_{\max}C = 0\ 1635\ \text{cm}^{-1}$.

Example 26

Trans-(±)-2-(benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide monohydrochloride

By Method D, (benzo[b]thien-3-yloxy)acetic acid (104 mg, 0.5 mmol) was converted to the amide. The crude product was purified by column chromatography on silica, using 1% triethylamine in 1:1 hexane/ethyl acetate as elutant. The resulting solution was evaporated and the residue dissolved in dichloromethane (3 ml). A solution of hydrogen chloride in diethyl ether was added until the solution became acidic, then diethyl ether added until precipitation was complete. The product was collected by filtration, washed with diethyl ether and dried in a vacuum oven at 70°C overnight to yield the amide monohydrochloride (49 mg, 24%); $V_{\max}C = 0\ 1660\ \text{cm}^{-1}$.

Example 27

Trans-(±)-N,5-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide monohydrochloride

By Method B 5-methylbenzo[b]thiophene-3-acetic acid (206 mg, 1 mmol) was converted to the amide monohydrochloride (349 mg, 86%); $V_{\max}C = 0\ 1640\ \text{cm}^{-1}$.

Example 28

Trans-(±)-5-chloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide monohydrochloride

By Method B, 5-chlorobenzo[b]thiophene-3-acetic acid (226.5 mg, 1 mmol) was converted to the amide monohydrochloride (374 mg, 87%); $V_{\max}C = 0\ 1635\ \text{cm}^{-1}$.

Trans-(±)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-acetamide

Indole-3-acetic acid (0.7 g, 4 mmol) was dissolved in tetrahydrofuran and carbonyl di-imidazole (0.7 g) added. The solution was boiled and allowed to stand for five minutes. *Trans-(±)-N-methyl-2-(1-pyrrolidinyl)cyclohexanamine* (0.73 g, 4 mmol) was added.

The solution was refluxed for five minutes, evaporated, and washed with excess saturated sodium bicarbonate solution. The solution was extracted three times with an ether/ethylacetate mixture, the

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combined extracts with water, dried (MgSO₄), and evaporated to give the *amide* as white plates (0.76 g, 56%) mp 189—190.5°C; V_{max}C = 0 1605 cm⁻¹.

Example 29

5 *Trans*-(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-*N*^o-oxide-benzo[b]thiophene-4-acetamide

A solution of *trans* - (±) - *N* - methyl - *N* - [2 - (1 - pyrrolidinyl) - cyclohexyl]benzo[b]thiophene - 4 - acetamide (0.41 g) in dichloromethane (10 ml) was treated with *m*-chloroperoxybenzoic acid (100 mg) and stirred at 0°C. After 50 minutes more *m*-chloroperoxybenzoic acid (153 mg) was added and after a total of 110 minutes the mixture was poured into saturated aqueous sodium bicarbonate (20 ml) and extracted
10 dichloromethane (2 × 10 ml) to give a white solid. Recrystallization (dichloromethane — diethyl ether) furnished pure *trans*(>) - *N* - methyl - *N* - [2 - (1 - pyrrolidinyl)cyclohexyl] - *N*^o - oxide - benzo[b]thiophene - 4 - acetamide (0.31 g, 72%), mp 149—151.5°C.

Example 30

15 *Trans*-(±)-*N*-methyl-*N*-(2-propynylamino)cyclohexylbenzo[b]thiophene-4-acetamide monohydrochloride

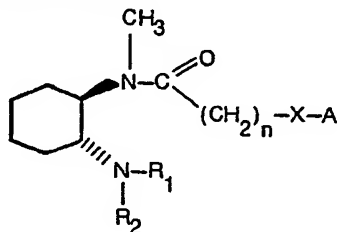
A solution of *trans* - (±) - *N* - methyl - *N* - (methylamino)cyclohexylbenzo[b]thiophene - 4 - acetamide monohydrochloride (450 mg) in dichloromethane (20 ml) was treated with saturated aqueous sodium bicarbonate to liberate the parent amine. This oil was dissolved in dichloromethane (2.5 ml) and treated with propargyl bromide (250 µl of an 80% solution in toluene) and triethylamine (0.20 ml). After 17
20 hours at room temperature, potassium carbonate (200 mg) and more dichloromethane (18 ml) were added. After 1.5 days the mixture was decanted and the supernatant was treated with propargyl bromide (150 µl of an 80% solution in toluene) at room temperature. After a further 12 hours this solution was poured into saturated aqueous sodium bicarbonate (20 ml) and extracted with dichloromethane (2 × 20 ml). Silica gel chromatography (4:1 ethyl acetate — methanol containing 1% triethylamine) furnished *trans* - (±) - *N* - methyl - *N* - [2 - (methyl(2 - propynyl)amino)cyclohexyl]benzo[b]thiophene - 4 - acetamide (220 mg,
25 49%). V_{max} liquid file 3300, 3225, 2110, 1630 cm⁻¹. The hydrochloride salt of this compound (220 mg) was prepared as described in Method L to give a white solid (230 mg, 93%).

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

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1. A compound having the structural formula

35



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wherein:

R₁ is methyl;

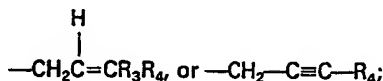
R₂ is hydrogen, alkyl

of from one to six carbon atoms,

45



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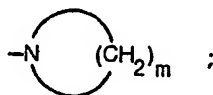


R₃ is hydrogen or methyl;

R₄ is hydrogen or methyl;

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or R₁ and R₂ taken together with the nitrogen atom to which they are attached form a ring denoted by



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m is an integer of from three to eight;

n is zero or an integer of from one to six;

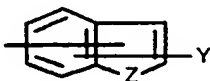
X is oxygen, sulphur, —CHR₅, or NR₆;

65

R₅ is hydrogen, alkyl of from one to six carbon atoms, or aryl;

R₆ is hydrogen or alkyl of from one to six carbon atoms;
A is

5



10 Y is hydrogen, fluorine, chlorine, alkyl or alkylene of from one to six carbon atoms, or aryl;
Z is oxygen, sulphur, —CH₂—, or NR₇; and R₇ is hydrogen, alkyl of from one to six carbon atoms, aryl,
or acyl of from 2 to 6 carbon atoms, or, when X is CHR₆, R₇ is the direct bond to X:
or an N¹-oxide of the compound of the foregoing structural formula;
a pharmaceutically acceptable acid addition salt of the compound of the foregoing structural formula
15 or its N¹-oxide.

2. A compound in accordance with Claim 1, wherein m is 4, 5 or 6; or a pharmaceutically acceptable acid addition salt thereof.

3. A compound in accordance with Claim 1, wherein n is 0, 1 or 2; or a pharmaceutically acceptable acid addition salt thereof.

20 4. A compound in accordance with Claim 1, selected from the N¹-oxides of compounds of structural formula I; and pharmaceutically acceptable acid addition salts thereof.

5. A compound in accordance with Claim 4 having the name *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]-N¹-oxide-benzo[*b*]-thiophene-4-acetamide.

6. A compound in accordance with Claim 1, wherein Z is oxygen, the compound being selected from:

25 *trans-N*-2,4-dimethyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofuranacetamide;

trans-N-methyl-phenyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacetamide;

and the pharmaceutically acceptable acid addition salts thereof.

7. A compound in accordance with Claim 1, wherein Z is sulphur, the compound being selected from:

30 *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-4-acetamide;

trans-N-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-3-acetamide;

trans-N-methyl-*N*-[2-(methylamino)cyclohexyl]benzo[*b*]thiophene-4-acetamide;

trans-N-methyl-*N*-[2-(methyl(2-propenyl)amino)cyclohexyl]benzo[*b*]thiophene-4-acetamide;

trans-N-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-*N*-methylbenzo[*b*]thiophene-4-acetamide;

trans-N-methyl-*N*-[methyl(2-propynyl)amino]cyclohexyl]benzo[*b*]thiophene-4-acetamide;

35 *trans-N*-methyl-7-propyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-4-acetamide;

trans-N-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thienyl)benzo[*b*]thiophene-7-acetamide;

trans-N-methyl-3-phenyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-5-acetamide;

trans-N-methyl-*N*-[2-(1-piperidinyl)cyclohexyl]benzo[*b*]thiophene-4-acetamide;

trans-N-methyl-*N*-[2-[methyl[(tetrahydro-2-furanyl)methyl]amino]cyclohexyl]benzo[*b*]thiophene-4-

40 acetamide;

trans-N-methyl-*N*-[2-methyl(3-methyl-2-butenyl)amino]cyclohexyl]benzo[*b*]thiophene-4-acetamide;

trans-N-[2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl]-*N*-methylbenzo[*b*]thiophene-4-

acetamide;

trans-N,5-dimethyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-3-acetamide;

45 *trans-N*-methyl-*N*-[2-[methyl(3-methyl-2-butenyl)amino]cyclohexyl]benzo[*b*]thiophene-4-acetamide;

trans-N-[2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl]-*N*-methylbenzo[*b*]thiophene-4-

acetamide;

trans-N,5-dimethyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-3-acetamide;

50 *trans*-5-chloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-3-acetamide;

trans-N-methyl-*N*-[2-pyrrolidinylcyclohexyl]-4-benzo[*b*]thiophene-2-propionamide;

trans-2-(benzo[*b*]thiophen-3-yloxy)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

and the pharmaceutically acceptable addition salts thereof.

8. A compound in accordance with Claim 1, wherein X is CH₂, the compound being selected from:

55 *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-3-acetamide;

trans-N-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indene-2-acetamide;

and the pharmaceutically acceptable acid addition salts thereof.

9. A compound in accordance with Claim 1, wherein X is NR₇, where R₇ is as defined in Claim 1, the compound being selected from:

60 *trans-N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-acetamide;

trans-N-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-propanamide;

trans-N-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-3-butanamide;

trans-N-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-indole-1-acetamide;

trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-*N*,2,3-trimethyl-1*H*-indole-5-acetamide;

trans-2,3,4,9-tetrahydro-*N*,9-dimethyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-carbazole-6-acetamide;

65 and the pharmaceutically acceptable acid addition salts thereof.

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10. A process for preparing a compound in accordance with Claim 1, the process comprising reacting a compound of the formula



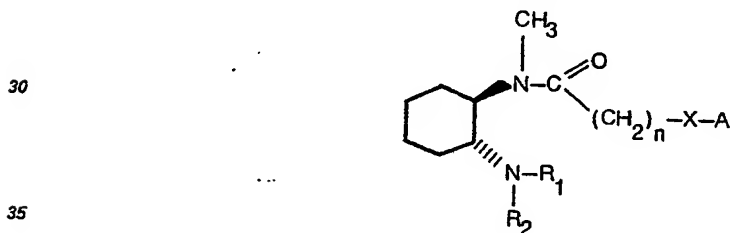
15 wherein R_1 and R_2 are as defined in Claim 1, with a carboxylic acid having the formula



wherein n , X , Y , and Z are as defined in Claim 1, or with a reactive carboxylic derivative of said acid.

11. A pharmaceutical composition useful for alleviating pain in a mammal, the composition comprising an effective amount of a compound in accordance with Claim 1 in combination with a pharmaceutically acceptable carrier.

25 12. A compound having the structural formula

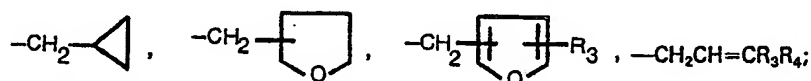


where:

R_1 is methyl;

R_2 is hydrogen, alkyl

40 of from one to six carbon atoms,



R_3 is hydrogen or methyl;

R_4 is hydrogen or methyl;

or R_1 and R_2 taken together with the nitrogen atom to which they are attached from a 5- or 6-membered ring;

n is zero or an integer of from one to six;

X is oxygen, sulphur, $-CHR_5$ or NR_5 ;

R_5 is hydrogen, alkyl of from one to six carbon atoms, or aryl;

R_6 is hydrogen or alkyl of from one to six carbon atoms;

A is



Y is hydrogen, fluorine, chlorine, alkyl of from one to six carbon atoms, or aryl;

Z is oxygen, sulphur, $-CH_2-$, or NR_7 ; and R_7 is hydrogen, alkyl of from one to six carbon atoms, aryl, or acyl of from 2 to 6 carbon atoms; or

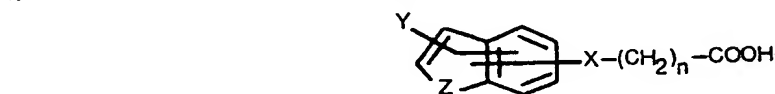
a pharmaceutically acceptable acid addition salt of the compound of the foregoing structural formula.

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13. A process for producing a compound in accordance with Claim 12, the process comprising reacting a compound of the formula



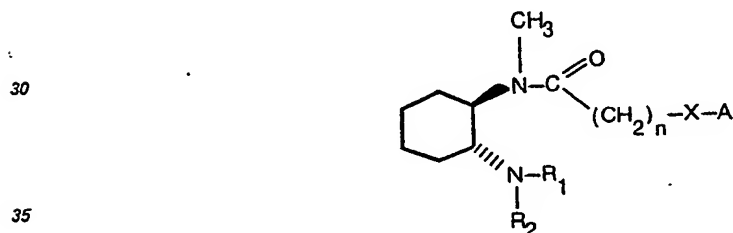
15 wherein R_1 and R_2 are as defined in Claim 12, with a carboxylic acid having the formula



wherein n , X , Y and Z are as defined in Claim 12, or with a reactive carboxylic derivative of said acid.

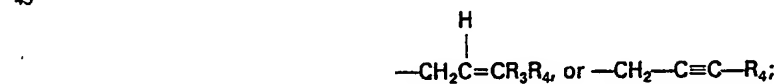
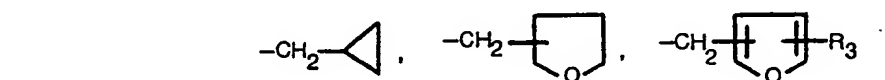
Claims for the Contracting State: AT

25 1. A process for producing a compound having the structural formula



where:

R_1 is methyl;
 R_2 is hydrogen, alkyl
 40 of from one to six carbon atoms,



R_3 is hydrogen or methyl;
 R_4 is hydrogen or methyl;
 or R_1 and R_2 taken together with the nitrogen atom to which they are attached form a ring denoted by



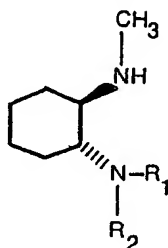
m is an integer of from three to eight;
 n is zero or an integer of from one to six;
 X is oxygen, sulphur, $-\text{CHR}_5$, or NR_6 ;
 60 R_5 is hydrogen, alkyl of from one to six carbon atoms, or aryl;
 R_6 is hydrogen or alkyl of from one to six carbon atoms;
 A is



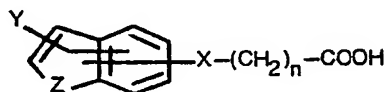
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Y is hydrogen, fluorine, chlorine, alkyl or alkylene of from one to six carbon atoms, or aryl;
Z is oxygen, sulphur, $-\text{CH}_2-$, or NR_7 ; and R_7 is hydrogen, alkyl of from one to six carbon atoms, aryl,
or acyl of from 2 to 6 carbon atoms, or, when X is CHR_6 , R_7 is the direct bond to X;
or an N^1 -oxide of the compound of the foregoing structural formula; or
a pharmaceutically acceptable acid addition salt of the compound of the foregoing structural formula
or its N^1 -oxide;

which process comprises reacting a compound of the formula



wherein R_1 and R_2 are as defined above, with a carboxylic acid having the formula



wherein n, X, Y, and Z are as defined above, or with a reactive carboxylic derivative of said acid: if necessary converting the compound to its N^1 -oxide; and if necessary converting the compound to an acid addition salt.

2. A process in accordance with Claim 1, wherein m is 4, 5 or 6; or a pharmaceutically acceptable acid addition salt thereof.

3. A process in accordance with Claim 1, wherein n is 0, 1 or 2; or a pharmaceutically acceptable acid addition salt thereof.

4. A process in accordance with Claim 1, for producing the N^1 -oxides of compounds of structural formula I; and pharmaceutically acceptable acid addition salts thereof.

5. A process in accordance with Claim 4 for producing *trans*-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]- N^1 -oxide-benzo[b]thiophene-4-acetamide.

6. A process in accordance with Claim 1, wherein Z is oxygen, for producing a compound selected from:

trans-N-2, dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofuranacetamide;
trans-N-methyl-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacetamide; ...
and the pharmaceutically acceptable acid addition salts thereof.

7. A process in accordance with Claim 1, wherein Z is sulphur, for producing a compound selected from:

trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-N-methyl-N-[2-(methylamino)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-[methyl(2-propenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-[2-[(cyclopropylmethyl)methylamino]cyclohexyl]-N-methylbenzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-[methyl(2-propynyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-7-propyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thienyl)benzo[b]thiophene-7-acetamide;
trans-N-methyl-3-phenyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-5-acetamide;
trans-N-methyl-N-[2-(1-piperidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-methyl-N-[2-[methyl[(tetrahydro-2-furanyl)methyl]amino]cyclohexyl]benzo[b]thiophene-4-acetamide;

trans-N-methyl-N-[2-methyl(3-methyl-2-butenyl)amino]cyclohexyl]benzo[b]thiophene-4-acetamide;
trans-N-[2-[(1,1-dimethyl-2-propenyl)methylamino]cyclohexyl]-N-methylbenzo[b]thiophene-4-acetamide;

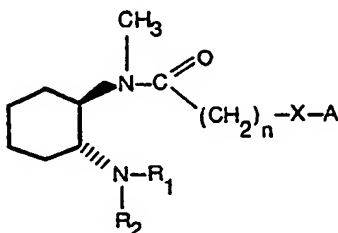
trans-N,5-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-5-chloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-3-acetamide;
trans-N-methyl-N-[2-pyrrolidinylcyclohexyl]-4-benzo[b]thiophene-2-propionamide;
trans-2-(benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acetamide;

and the pharmaceutically acceptable addition salts thereof.

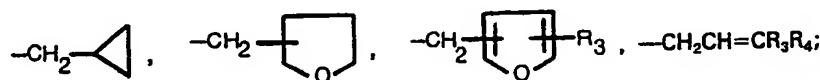
8. A process in accordance with Claim 1, wherein X is CH₂, for producing a compound selected from:
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indene-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indene-2-acetamide;
 and the pharmaceutically acceptable acid addition salts thereof.

9. A process in accordance with Claim 1, wherein X is NR₇, where R₇ is as defined in Claim 1, for producing a compound selected from:
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-acetamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-propanamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-butanamide;
trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-1-acetamide;
trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N,2,3-trimethyl-1H-indole-5-acetamide;
trans-2,3,4,9-tetrahydro-N,9-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-carbazole-6-acetamide;
 and the pharmaceutically acceptable acid addition salts thereof.

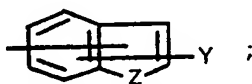
10. A process for producing a compound having the structural formula



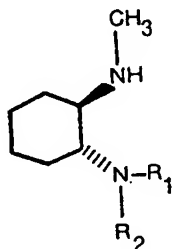
R_1 is methyl;
 R_2 is hydrogen, alkyl
 of from one to six carbon atoms,



40 n is zero or an integer of from one to six;
X is oxygen, sulphur, $-\text{CHR}_5$ or NR_6 ;
 R_5 is hydrogen, alkyl of from one to six carbon atoms, or aryl;
 R_6 is hydrogen or alkyl of from one to six carbon atoms;
A is



50 Y is hydrogen, fluorine, chlorine, alkyl of from one to six carbon atoms, or aryl;
Z is oxygen, sulphur, $-\text{CH}_2-$, or NR_7 ; and
R₇ is hydrogen, alkyl of from one to six carbon atoms, aryl, or acyl of from 2 to 6 carbon atoms; or
a pharmaceutically acceptable acid addition salt of the compound of the foregoing structural formula:
the process comprising reacting a compound of the formula



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wherein R_1 and R_2 are as defined above, with a carboxylic acid having the formula



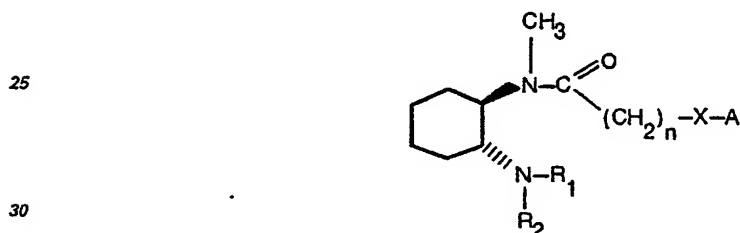
10 wherein n , X , Y and Z are as defined above, or with a reactive carboxylic derivative of said acid.

11. A process for producing a pharmaceutical composition, which comprises admixing a compound as produced in accordance with Claim 1, with a pharmaceutically acceptable carrier or diluent.

15

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

20 1. Verbindung der Strukturformel

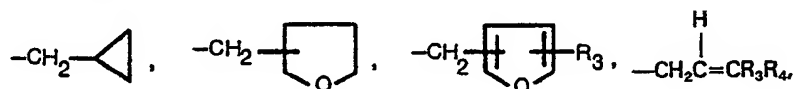


worin:

R_1 Methyl ist;

R_2 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen,

35



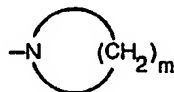
40 oder $-CH_2-C\equiv C-R_4$ steht;

R_3 für Wasserstoff oder Methyl steht;

R_4 für Wasserstoff oder Methyl steht; oder

R_1 und R_2 , wenn sie mit dem Stickstoffatom, an welches sie gebunden sind, zusammengekommen werden, einen Ring, gekennzeichnet

45



50 bilden;

m eine ganze Zahl von 3 bis 8 ist;

n für Null oder eine ganze Zahl von 1 bis 6 steht;

X für Sauerstoff, Schwefel, $-CHR_5$ oder NR_6 steht;

R_5 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;

55

R_6 für Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen steht;

A ist:

60



Y für Wasserstoff, Fluor, Chlor, Alkyl oder Alkylen mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;

Z für Sauerstoff, Schwefel, $-CH_2-$ oder NR_7 steht; und worin

R Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Aryl oder Acyl mit 2 bis 6 Kohlenstoffatomen ist

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oder wenn X für CHR_5 steht, R_7 die direkte Bindung an X bedeutet;

oder ein N¹-Oxid der Verbindung der oben stehenden Strukturformel;
oder ein pharmazeutisch akzeptables Säureadditionssalz der Verbindung der oben stehenden
Strukturformel oder sein N¹-Oxid.

2. Verbindung nach Anspruch 1, worin m für 4, 5 oder 6 steht; oder ein pharmazeutisch akzeptables
Säureadditionssalz davon.

3. Verbindung nach Anspruch 1, worin n für 0, 1 oder 2 steht; oder ein pharmazeutisch akzeptables
Säureadditionssalz davon.

4. Verbindung nach Anspruch 1, ausgewählt aus den N¹-Oxiden der Verbindungen der Strukturformel
I; und pharmazeutisch akzeptable Säureadditionssalze davon.

5. Verbindung nach Anspruch 4 mit dem Namen *trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N¹-
oxid-benzo[b]-thiophen-4-acetamid.

6. Verbindung nach Anspruch 1, worin Z für Sauerstoff steht, wobei die Verbindung ausgewählt ist
aus:

trans-N-2,5-Dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-3-benzofuranacetamid;
trans-N-Methyl-phenyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-5-benzofuranacetamid;
und die pharmazeutisch akzeptablen Säureadditionssalze davon.

7. Verbindung nach Anspruch 1, worin Z für Schwefel steht, wobei die Verbindung ausgewählt ist aus:

trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-3-acetamid;
trans-N-Methyl-N-[2-(methylamino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(methyl-(2-propenyl)-amino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-[2-((Cyclopropylmethyl)-methylamino)-cyclohexyl]-N-methylbenzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(methyl-(2-propenyl)-amino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-7-propyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-3-(2-thienyl)-benzo[b]-thiophen-7-acetamid;
trans-N-Methyl-3-phenyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-5-acetamid;
trans-N-Methyl-N-[2-(1-piperidinyl)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-Methyl-N-[2-(methyl-[(tetrahydro-2-furanyl)-methyl]-amino)-cyclohexyl]-benzo[b]-thiophen-4-
acetamid;

trans-N-Methyl-N-[2-methyl-(3-methyl-2-butenyl)amino]-cyclohexyl]-benzo[b]-thiophen-4-acetamid;
trans-N-[2-((1,1-Dimethyl-2-propenyl)-methylamino)-cyclohexyl]-N-methylbenzo[b]-thiophen-4-
acetamid;

trans-N,5-Dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[b]-thiophen-3-acetamid;
trans-N-Methyl-N-[2-(Methyl-(3-methyl-2-butenyl)-amino)-cyclohexyl]benzo[b]-thiophen-4-acetamid;
trans-N-[2-((1,1-Dimethyl-2-propenyl)-methylamino)-cyclohexyl]-N-methylbenzo[b]-thiophen-4-
acetamid;

trans-N,5-Dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[b]-thiophen-3-acetamid;
trans-5-Chlor-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[b]-thiophen-3-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-4-benzo[b]-thiophen-2-propionamid;
trans-2-(Benzo[b]-thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-acetamid;

und die pharmazeutisch akzeptablen Säureadditionssalze davon.

8. Verbindung nach Anspruch 1, worin X für CH₂ steht, wobei die Verbindung ausgewählt ist aus:

trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-inden-3-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-inden-2-acetamid;

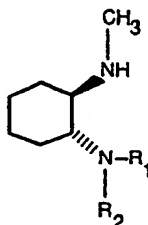
und die pharmazeutisch akzeptablen Säureadditionssalze davon.

9. Verbindung nach Anspruch 1, worin X für NR₇ steht, worin R₇ wie im Anspruch 1 definiert ist, wobei
die Verbindung ausgewählt ist aus:

trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-acetamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-propanamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-butanamid;
trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-1-acetamid;
trans-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N,2,3-trimethyl-1*H*-indol-5-acetamid;
trans-2,3,4,9-Tetrahydro-N,9-dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-carbazol-6-acetamid;

und die pharmazeutisch akzeptablen Säureadditionssalze davon.

10. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, welches Verfahren umfaßt:
die Umsetzung einer Verbindung der Formel



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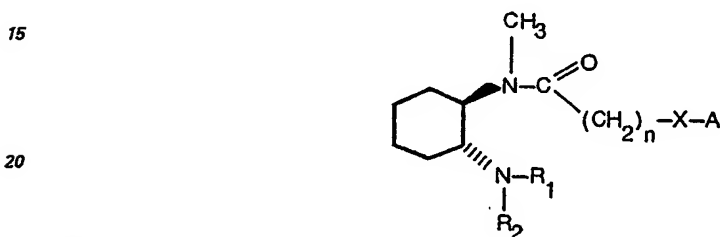
worin R_1 und R_2 wie in Anspruch 1 definiert sind, mit einer Carbonsäure der Formel



worin n , X , Y und Z wie in Anspruch 1 definiert sind, oder mit einem reaktiven Carbonsäure-Derivat dieser Säure.

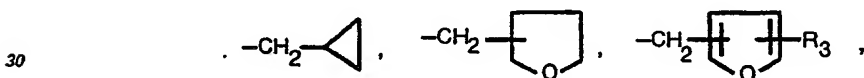
10 11. Pharmazeutische Zusammensetzung, welche zur Linderung von Schmerz bei einem Säuger nützlich ist, welche Zusammensetzung eine wirksame Menge einer Verbindung nach Anspruch 1 in Kombination mit einem pharmazeutisch akzeptablen Träger umfaßt.

12. Verbindung der Strukturformel



worin

25 R_1 für Methyl steht;
 R_2 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen,



— $CH_2CH=CR_3R_4$ ist;

R_3 für Wasserstoff oder Methyl steht;

R_4 für Wasserstoff oder Methyl steht; oder

35 R_1 und R_2 , wenn sie mit dem Stickstoffatom, an welches sie gebunden sind, zusammengenommen werden, einen 5- oder 6-gliedrigen Ring bilden;

n für Null oder eine ganze Zahl von 1 bis 6 steht;

X Sauerstoff, Schwefel, — CHR_5 oder NR_6 ist;

R_5 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;

40 R_6 Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen ist;

A ist:



Y für Wasserstoff, Fluor, Chlor, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;

Z Sauerstoff, Schwefel, — CH_2 — oder NR_7 ist; und

R_7 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Aryl oder Acyl mit 2 bis 6 Kohlenstoffatomen steht; oder

50 ein pharmazeutisch akzeptables Säureadditionssalz der Verbindung der obigen Strukturformel.

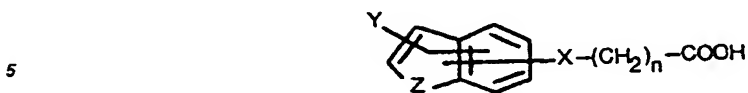
13. Verfahren zur Herstellung einer Verbindung nach Anspruch 12, welches Verfahren umfaßt: die Umsetzung einer Verbindung der Formel



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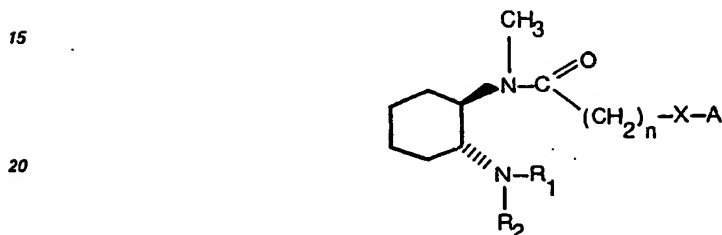
worin R_1 und R_2 wie im Anspruch 12 definiert sind, mit einer Carbonsäure der Formel



worin n , X , Y und Z wie im Anspruch 12 definiert sind, oder mit einem reaktiven carboxylischem Derivat dieser Säure.

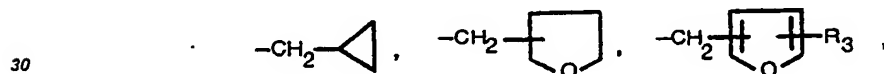
10 Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Strukturformel



worin:

- 25 R_1 für Methyl steht;
 R_2 für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen,



oder $-\text{CH}_2-\text{C}\equiv\text{C}-\text{R}_4$ steht;

- 35 R_3 Wasserstoff oder Methyl ist;
 R_4 für Wasserstoff oder Methyl steht; oder
 R_1 und R_2 , wenn sie mit dem Stickstoffatom, an welches sie gebunden sind, zusammengekommen werden, einen Ring, gekennzeichnet



bilden;

- 45 m eine ganze Zahl von 3 bis 8 ist;
 n für Null oder eine ganze Zahl von 1 bis 6 steht;
 X für Sauerstoff, Schwefel, $-\text{CHR}_5$ oder NR_6 steht;
 R_5 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl ist;
 R_6 für Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen steht;
 A für:

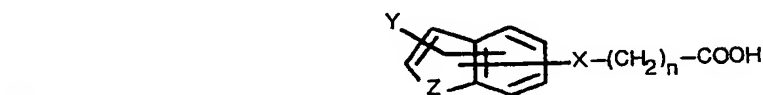


- 55 Y für Wasserstoff, Fluor, Chlor, Alkyl oder Alkylen mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;
 Z für Sauerstoff, Schwefel, $-\text{CH}_2-$ oder NR_7 steht; und
 R_7 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Aryl oder Acyl mit 2 bis 6 Kohlenstoffatomen ist
oder wenn X für CHR_5 steht, R_7 die direkte Bindung an X bedeutet;
oder eines N^1 -Oxids der Verbindung der oben stehenden Strukturformel;
60 oder eines pharmazeutisch akzeptablen Säureadditionssalzes der Verbindung der oben stehenden Strukturformel oder ihres N^1 -Oxids;
welches Verfahren umfaßt:

die Umsetzung einer Verbindung der Formel



15 worin R₁ und R₂ wie oben definiert sind, mit einer Carbonsäure der Formel



worin n, X, Y und Z wie oben definiert sind, oder mit einem reaktiven carboxylischem Derivat dieser Säure; falls erforderlich Überführen der Verbindung in ihr N¹-Oxid; und falls erforderlich Überführen der Verbindung in ein Säureadditionssalz.

2. Verfahren nach Anspruch 1, worin m für 4, 5 oder 6 steht; oder ein pharmazeutisch akzeptables Säureadditionssalz davon.

3. Verfahren nach Anspruch 1, worin n für 0, 1 oder 2 steht; oder ein pharmazeutisch akzeptables Säureadditionssalz davon.

4. Verfahren nach Anspruch 1, zur Herstellung der N¹-Oxide der Verbindungen der Strukturformel I; und pharmazeutisch akzeptablen Säureadditionssalze davon.

5. Verfahren nach Anspruch 4 zur Herstellung von *trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N¹-oxid-benzo[b]-thiophen-4-acetamid.

6. Verfahren nach Anspruch 1, worin Z Sauerstoff ist, zur Herstellung einer Verbindung, welche ausgewählt ist aus:

trans-N-2,2-Dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-3-benzofuranacetamid;

trans-N-Methyl-phenyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-5-benzofuranacetamid;

und der pharmazeutisch akzeptablen Säureadditionssalze davon.

7. Verfahren nach Anspruch 1, worin Z Schwefel ist, zur Herstellung einer Verbindung ausgewählt aus:

trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-3-acetamid;

trans-N-Methyl-N-[2-(methylamino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-(methyl-(2-propenyl)-amino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-[2-[(Cyclopropylmethyl)-methylamino]-cyclohexyl]-N-methylbenzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-(methyl-(2-propenyl)-amino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-7-propyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-3-(2-thienyl)-benzo[b]-thiophen-7-acetamid;

trans-N-Methyl-3-phenyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzo[b]-thiophen-5-acetamid;

trans-N-Methyl-N-[2-(1-piperidinyl)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-(methyl-[(tetrahydro-2-furanyl)-methyl]-amino)-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-Methyl-N-[2-methyl-(3-methyl-2-butenyl)amino]-cyclohexyl]-benzo[b]-thiophen-4-acetamid;

trans-N-[2-[(1,1-Dimethyl-2-propenyl)-methylamino]-cyclohexyl]-N-methylbenzo[b]thiophen-4-acetamid;

trans-N,5-Dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[b]-thiophen-3-acetamid;

trans-N-Methyl-N-[2-(methyl-(3-methyl-2-butenyl)-amino)-cyclohexyl]benzo[b]-thiophen-4-acetamid;

trans-N-[2-[(1,1-Dimethyl-2-propenyl)-methylamino]-cyclohexyl]-N-methylbenzo[b]-thiophen-4-

acetamid;

trans-N,5-Dimethyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[b]-thiophen-3-acetamid;

trans-5-Chlor-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzo[b]-thiophen-3-acetamid;

trans-N-Methyl-N-[2-(pyrrolidinyl)cyclohexyl]-4-benzo[b]thiophen-2-propionamid;

trans-2-(Benzo[b]thiophen-3-yloxy)-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-acetamid;

und der pharmazeutisch akzeptablen Additionsalze davon.

8. Verfahren nach Anspruch 1, worin X für CH₂ steht, zur Herstellung einer Verbindung ausgewählt aus:

trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-inden-3-acetamid;

trans-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-inden-2-acetamid;

und der pharmazeutisch akzeptablen Säureadditionssalze davon.

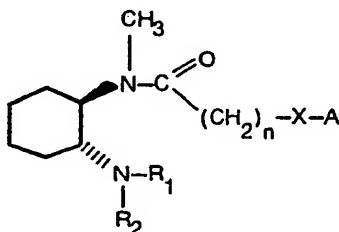
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9. Verfahren nach Anspruch 1, worin X für NR₇ steht, worin R₇, wie im Anspruch 1 definiert ist, zur Herstellung einer Verbindung welche ausgewählt ist aus:

- trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-acetamid;
- trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-propanamid;
- trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-3-butanamid;
- trans*-N-Methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-1*H*-indol-1-acetamid;
- trans*-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N,2,3-trimethyl-1*H*-indol-5-acetamid;
- trans*-2,3,4,9-Tetrahydro-N,9-dimethyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1*H*-carbazol-6-acetamid;

und der pharmazeutisch akzeptablen Säureadditionssalze davon.

10. Verfahren zur Herstellung einer Verbindung der Strukturformel



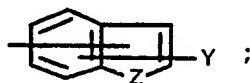
worin

- R₁ für Methyl steht;
- R₂ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen,

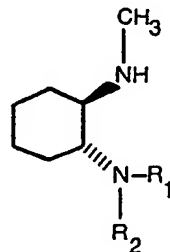


-CH₂CH=CR₃R₄ ist;

- R₃ für Wasserstoff oder Methyl steht;
- R₄ für Wasserstoff oder Methyl steht; oder
- R₁ und R₂, wenn sie mit dem Stickstoffatom, an welches sie gebunden sind, zusammengenommen werden, einen 5- oder 6-gliedrigen Ring bilden;
- n für Null oder eine ganze Zahl von 1 bis 6 steht;
- X für Sauerstoff, Schwefel, -CHR₅ oder NR₆ steht;
- R₅ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl ist;
- R₆ Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen ist;
- A ist:



- Y für Wasserstoff, Fluor, Chlor, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Aryl steht;
- Z Sauerstoff, Schwefel, -CH₂- oder NR₇ ist; und
- R₇ für Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Aryl oder Acyl mit 2 bis 6 Kohlenstoffatomen steht; oder
- eines pharmazeutisch akzeptablen Säureadditionssalzes der Verbindung der oben stehenden Strukturformel;
- welches Verfahren umfaßt:
- die Umsetzung einer Verbindung der Formel



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worin R_1 und R_2 wie oben definiert sind, mit einer Carbonsäure der Formel

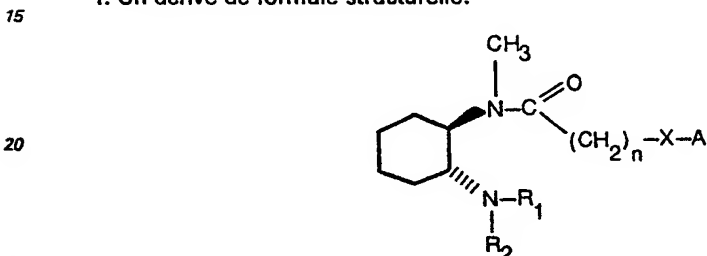


worin n , X , Y und Z wie oben definiert sind, oder mit einem reaktiven carboxylischem Derivat dieser Säure.

11. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welches das Mischen einer nach Anspruch 1 hergestellten Verbindung mit einem pharmazeutisch akzeptablen Träger oder Verdünnungsmittel umfaßt.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

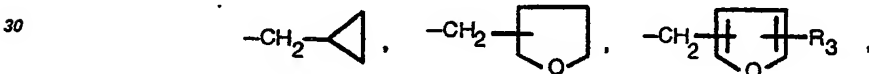
1. Un dérivé de formule structurelle:



25 dans laquelle:

R_1 représente le radical méthyle; et

R_2 représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone,



$-\text{CH}_2\text{CH}=\text{CR}_3\text{R}_4$ ou $-\text{CH}_2-\text{C}\equiv\text{C}-\text{R}_4$, R_3 et R_4 représentant indépendamment un atome d'hydrogène ou un radical méthyle; ou dans laquelle

35 R_1 et R_2 , pris ensemble en même temps que l'atome d'azote auquel ils sont attachés, forment un cycle répondant au schéma:



dans lequel

m est un nombre entier de 3 à 8;

n est un entier de 0 à 6;

45 X représente un atome d'oxygène, de soufre ou CHR_5 , dans lequel R_5 représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

ou X représente NR_6 , R_6 étant un atome d'hydrogène ou un radical alkyle renfermant de 1 à 6 atomes de carbone;

A représentant:



où:

55 Y représente un atome d'hydrogène, de fluor, de chlore, un radical alkyle ou alkylène renfermant de 1 à 6 atomes de carbone ou un radical aryle; et

Z représente un atome d'oxygène, de soufre, $-\text{CH}_2-$ ou NR_7 , R_7 étant un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone, aryle ou acyle renfermant de 2 à 6 atomes de carbone

60 où, lorsque X représente CHR_5 , R_7 représente la liaison directe avec X ;

2. Un dérivé selon la revendication 1, dans lequel m est égal à 4, 5 ou 6 ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

3. Un dérivé selon la revendication 1, dans lequel n est égal à 0, 1 ou 2, ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

4. Un dérivé selon la revendication 1, choisi parmi les N¹-oxydes des dérivés de formule structurelle I, et leurs sels d'addition d'acides pharmaceutiquement acceptables.

5. Un dérivé selon la revendication 4, désigné sous le nom de: trans-N-méthyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-N¹-oxyde-benzo[b]thiophène-4-acétamide.

6. Un dérivé selon la revendication 1, dans lequel Z représente un atome d'oxygène, le dérivé étant choisi parmi les suivants:

trans-N-2-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofurmacétamide;
trans-N-méthyl-phényl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacétamide;

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

7. Un dérivé selon la revendication 1, dans lequel Z représente le soufre, le dérivé étant choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;
trans-N-méthyl-N-[2-(méthylamino)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-(méthyl(2-propényl)amino)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-[2-[(cyclopropylméthyl)méthylamino]cyclohexyl]-N-méthylbenzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-(méthyl(2-propényl)amino)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-7-propyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thiényl)benzo[b]thiophène-7-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-5-acétamide;
trans-N-méthyl-N-[2-(1-pipéridinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-méthyl-N-[2-méthyl[(tétrahydro-2-furanyl)méthyl]amino]cyclohexyl]benzo[b]thiophène-4-

acétamide;

trans-N-méthyl-N-[2-méthyl-(3-méthyl-2-butényl)-amino-cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-[2-[(1,1-diméthyl-2-propényl)méthylamino]cyclohexyl]-N-méthylbenzo[b]thiophène-4-

acétamide;

trans-N-5-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;
trans-N-méthyl-N-[2-(méthyl(3-méthyl-2-butényl)amino)cyclohexyl]benzo[b]thiophène-4-acétamide;
trans-N-[2-[(1,1-diméthyl-2-propényl)méthylamino]cyclohexyl]-N-méthylbenzo[b]thiophène-4-

acétamide;

trans-N-5-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;
trans-5-chloro-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;
trans-N-méthyl-N-[2-(pyrrolidinyl)cyclohexyl]-4-benzo[b]thiophène-2-propionamide;
trans-2-(benzo[b]thiophène-3-yloxy)-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acétamide;

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

8. Un dérivé selon la revendication 1, dans lequel X représente CH₂, le dérivé étant choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indène-3-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indène-2-acétamide;

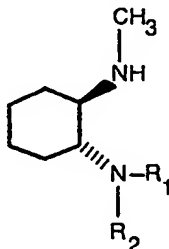
et leurs sels d'addition d'acides pharmaceutiquement acceptables.

9. Un dérivé selon la revendication 1, dans lequel X représente NR₇, R₇ étant tel que défini dans la revendication 1, le dérivé étant choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-acétamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-propanamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-butanamide;
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-1-acétamide;
trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N-2,3-triméthyl-1H-indole-5-acétamide;
trans-2,3,4,9-tétrahydro-N-9-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-carbazole-6-acétamide;

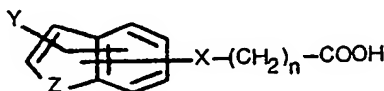
et leurs sels d'addition d'acides pharmaceutiquement acceptables.

10. Un procédé de préparation d'un dérivé en accord avec la revendication 1, ce procédé consistant à faire réagir un dérivé de formule:



dans laquelle:

R₁ et R₂ sont tels que définis dans la revendication 1; avec un acide carboxylique répondant à la formule:



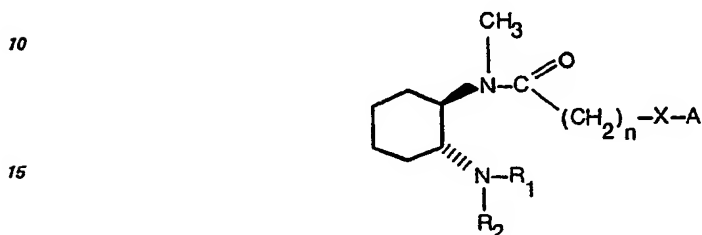
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dans laquelle:

n, X, Y et Z sont tels que définis dans la revendication 1, ou avec un dérivé carboxylique réactif de cet acide.

11. Une composition pharmaceutique utile pour soulager la douleur d'un mammifère, cette composition comprenant une quantité efficace d'un dérivé selon la revendication 1, en association avec un support pharmaceutiquement acceptable.

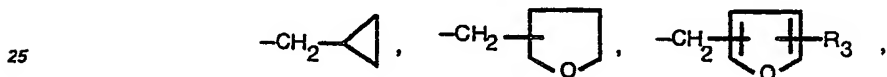
12. Un dérivé de formule structurelle:



dans laquelle:

20 R₁ représente le radical méthyle;

R₂ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone;



—CH₂CH=CR₃R₄ ou —CH₂—C≡C—R₄,

R₃ représente un atome d'hydrogène ou le radical méthyle;

30 R₄ représente un atome d'hydrogène ou le radical méthyle;

ou R₁ et R₂, pris ensemble en même temps que l'atome d'azote auquel ils sont attachés, forment un cycle à 5 ou 6 éléments;

n est égal à 0 ou un nombre entier de 1 à 6, bornes comprises;

X représente un atome d'oxygène, de soufre, CHR₅, ou NR₆,

35 R₅ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

R₆ représente un atome d'hydrogène ou un radical alkyle renfermant de 1 à 6 atomes de carbone;

A représente:



45 Y représente un atome d'hydrogène, de fluor, de chlore, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

Z représente un atome d'oxygène, de soufre, —CH₂— ou NR₇, R₇ étant un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone, aryle ou acyle renfermant de 2 à 6 atomes de carbone;

50 ou un sel d'addition d'acide pharmaceutiquement acceptable du dérivé répondant à la formule structurelle précédente.

13. Un procédé de préparation d'un dérivé selon la revendication 12, ce procédé consistant à faire réagir un dérivé de formule:



65 dans laquelle R₁ et R₂ sont tels que définis dans la revendication 12;

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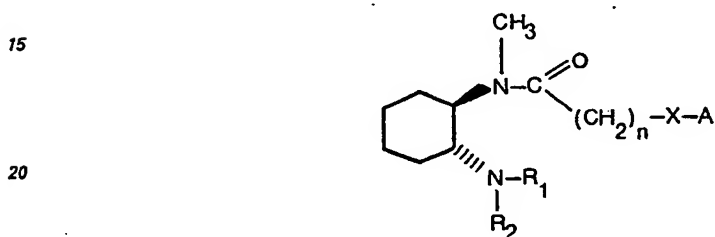
avec un acide carboxlique de formule:



dans laquelle n, X, Y et Z sont tels que définis dans la revendication 12, ou avec un dérivé carboxylique réactif de cet acide.

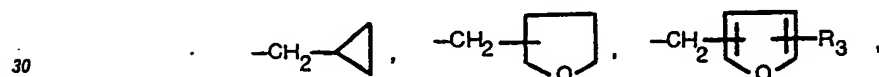
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1. Un procédé de préparation d'un dérivé de formule structurelle:



dans laquelle:

25 R_1 représente le radical méthyle; et
 R_2 représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone,



—CH₂CH=CR₃R₄ ou —CH₂—C≡C—R₄, R₃ et R₄ représentant indépendamment un atome d'hydrogène ou un radical méthyle;
 35 ou dans laquelle R₁ et R₂, pris ensemble en même temps que l'atome d'azote auquel ils sont attachés, forment un cycle répondant au schéma:



dans lequel m est un nombre entier de 3 à 8;

n est un entier de 0 à 6;

45 X représente un atome d'oxygène, de soufre ou CHR₅, dans lequel R₅ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

ou X représente NR₆, R₆ étant un atome d'hydrogène ou un radical alkyle renfermant de 1 à 6 atomes de carbone;

A représentant:



ou:

55 Y représente un atome d'hydrogène, de fluor, de chlore, un radical alkyle ou alkylène renfermant de 1 à 6 atomes de carbone ou un radical aryle; et

Z représente un atome d'oxygène, de soufre, —CH₂— ou NR₇, R₇ étant un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone, aryle ou acyle renfermant de 2 à 6 atomes de carbone où, lorsque X représente CHR₅, R₇ représente la liaison directe avec X;

60 ou un N¹-oxyde du dérivé de formule structurelle suivante; ou un sel d'addition d'acide pharma-

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ceutiquement acceptable du dérivé de formule structurelle ci-dessus ou de son N¹-oxyde; ce procédé consistant à faire réagir un dérivé de formule:



15 dans laquelle R₁ et R₂ sont tels que définis ci-dessus; avec un acide carboxylique de formule:



dans laquelle n, X, Y et Z sont tels que définis ci-dessus; ou avec un dérivé carboxylique réactif de cet acide et, si nécessaire, on convertit le dérivé en son N¹-oxyde et, si nécessaire, on convertit le dérivé en un sel d'addition d'acide.

2. Un procédé selon la revendication 1, dans lequel m est égal à 4, 5 ou 6 ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

3. Un procédé selon la revendication 1, dans lequel n est égal à 0, 1 ou 2, ou un de ses sels d'addition d'acides pharmaceutiquement acceptables.

4. Un procédé selon la revendication 1 de préparation des N¹-oxydes des dérivés de formule structurelle I, et leurs sels d'addition d'acides pharmaceutiquement acceptables.

5. Un procédé selon la revendication 4 de préparation de trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-N¹-oxyde-benzo[b]thiophène-4-acétamide.

6. Un procédé selon la revendication 1, dans lequel Z représente un atome d'oxygène, de préparation d'un dérivé choisi parmi:

trans-N-2-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-benzofuranacétamide;

trans-N-méthyl-phényl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-benzofuranacétamide;

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

7. Un procédé selon la revendication 1, dans lequel Z représente le soufre, de préparation d'un dérivé étant choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;

trans-N-méthyl-N-[2-(méthylamino)cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-[méthyl-(2-propényl)amino]cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-[2-[(cyclopropylméthyl)méthylamino]cyclohexyl]-N-méthylbenzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-[méthyl-(2-propényl)amino]cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-3-(2-thiényl)benzo[b]thiophène-7-acétamide;

trans-N-méthyl-N-[2-(1-pipéridinyl)cyclohexyl]benzo[b]thiophène-5-acétamide;

trans-N-méthyl-N-[2-méthyl-[[tétrahydro-2-furanyl]méthyl]amino]cyclohexyl]benzo[b]thiophène-4-

acétamide;

trans-N-méthyl-N-[2-méthyl-(3-méthyl-2-butényl)-amino-cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-[2-[[1,1-diméthyl-2-propényl]méthylamino]cyclohexyl]-N-méthylbenzo[b]thiophène-4-

acétamide;

trans-N-5-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;

trans-N-méthyl-N-[2-[méthyl(3-méthyl-2-butényl)amino]cyclohexyl]benzo[b]thiophène-4-acétamide;

trans-N-[2-[[1,1-diméthyl-2-propényl]méthylamino]cyclohexyl]-N-méthylbenzo[b]thiophène-4-

acétamide;

trans-N-5-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;

trans-5-chloro-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophène-3-acétamide;

trans-N-méthyl-N-(2-pyrrolidinylcyclohexyl)-4-benzo[b]thiophène-2-propionamide;

trans-2-(benzo[b]thiophène-3-yloxy)-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]acétamide;

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

8. procédé dérivé selon la revendication 1, dans lequel X représente CH₂, de préparation d'un dérivé choisi parmi:

trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indène-3-acétamide;

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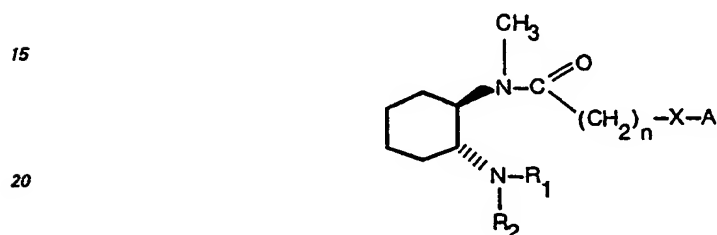
trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indène-2-acétamide;
et leurs sels d'addition d'acides pharmaceutiquement acceptables.

9. Un procédé selon la revendication 1, dans lequel X représente NR₇, R₇ étant tel que défini dans la revendication 1, de préparation d'un dérivé choisi parmi:

- trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-acétamide;
- trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-propanamide;
- trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-3-butanamide;
- trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-indole-1-acétamide;
- trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N-2,3-triméthyl-1H-indole-5-acétamide;
- trans-2,3,4,9-tétrahydro-N-9-diméthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1H-carbazole-6-acétamide;

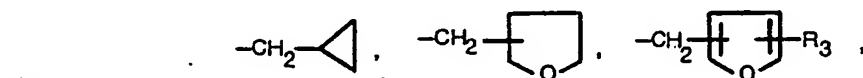
et leurs sels d'addition d'acides pharmaceutiquement acceptables.

10. Un procédé de préparation d'un dérivé de formule structurelle:



dans laquelle:

- R₁ représente le radical méthyle;
- R₂ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone;



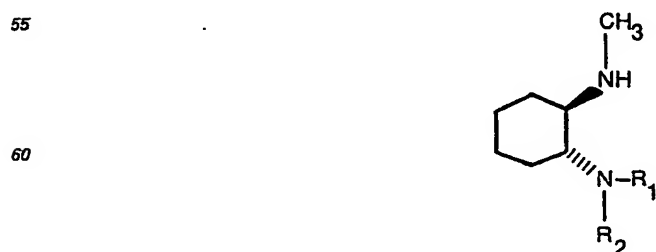
—CH₂CH=CR₃R₄ ou —CH₂—C≡C—R₄,

- R₃ représente un atome d'hydrogène ou le radical méthyle;
- R₄ représente un atome d'hydrogène ou le radical méthyle;
- ou R₁ et R₂, pris ensemble en même temps que l'atome d'azote auquel ils sont attachés, forment un cycle à 5 ou 6 éléments;
- n est égal à 0 ou un nombre entier de 1 à 6, bornes comprises;
- X représente un atome d'oxygène, de soufre, CHR₅, ou NR₆;
- R₅ représente un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;
- R₆ représente un atome d'hydrogène ou un radical alkyle renfermant de 1 à 6 atomes de carbone;
- A représente:



Y représente un atome d'hydrogène, de fluor, de chlore, un radical alkyle renfermant de 1 à 6 atomes de carbone ou un radical aryle;

- Z représente un atome d'oxygène, de soufre, —CH₂— ou NR₇, R₇ étant un atome d'hydrogène, un radical alkyle renfermant de 1 à 6 atomes de carbone, aryle ou acyle renfermant de 2 à 6 atomes de carbone;
- ou un sel d'addition d'acide pharmaceutiquement acceptable du dérivé répondant à la formule structurelle ci-dessus, ce procédé consistant à faire réagir un dérivé de formule:



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dans laquelle R_1 et R_2 sont tels que définis ci-dessus; avec un acide carboxylique de formule:



dans laquelle n , X , Y et Z sont tels que définis ci-dessus; ou avec un dérivé carboxylique réactif de cet acide.

11. Un procédé de préparation d'une composition pharmaceutique, qui consiste à mélanger un dérivé obtenu selon la revendication 1, avec un support ou diluant pharmaceutiquement acceptable.

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